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Article

Mechanistic Insights of Resolution of Inflammation by Endogenous Lipid Mediators

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ABSTRACT

Inflammation is an essential part of the body's healing process. Yet a long-term or chronic inflammatory response is damaging and is linked with several adult human diseases such as heart ailments, diabetes, cancer, asthma, and arthritis. The current therapeutic approach targets the pro-inflammatory mediators by using several commercially available anti-inflammatory drugs or monoclonal antibodies to combat these chronic inflammatory diseases. Although these current approaches seem to be effective, they often fail to provide a 'total therapeutic solution' and thereby complicating the situation and ultimately increasing the infection risk. In this context, the concepts and mechanisms of the resolution could be helpful for treating these chronic inflammatory diseases. The review is devoted to the mechanism of inflammation resolution and the working procedure of the specialized pro-resolving lipid mediators like maresins, lipoxins, resolvins, and protectins. Alongside these standard specialized pro-resolving lipid mediators, plant-based lipid mediators in the form of biflavonoids have also emerged as an alternative option, which can limit the inflammatory response by targeting 5-lipoxygenase and also by triggering the switching of leukotrienes to specialized pro-resolving mediators. Other plant-based mediators will also strengthen the approach to the resolution of chronic inflammatory diseases.

1. INTRODUCTION

Inflammation, a complex biological process or response of the immune system which acts against harmful stimuli, like pathogens, toxic compounds, damaged cells or irradiation. It is protective in nature that engages blood vessels, immune cells, and molecular mediators. It is an essential immune activity by the host to get rid of the harmful stimulus and initiate the healing process of damaged tissue. Inflammation, therefore, is a defense mechanism that makes a vital role in maintaining cellular homeostasis (Medzhitov 2008). Inflammation principally serves by eliminating the primary cause of cell damage, removing damaged tissue, and initiating the tissue-repairing process.

Inflammation can be generally classified into 2 main types: acute and chronic, based on its time course (Medzhitov 2008). Acute inflammation is the most important and immediate host-protective response of our body against any unsafe stimuli and often serves as the 'first line of defense'. It is attained by the movement of plasma and immune cells from the blood into the damaging tissues that last for a few days (Medzhitov 2008; Ashley et al. 2012). However, when acute inflammatory response remains unresolved it leads to the progressive shift of various molecular cells at the site of inflammation. This prolonged immune response is characterized by simultaneous tissue-destruction that results in the emergence of severe chronic diseases like heart ailments, diabetes, cancer, asthma, and arthritis (Medzhitov 2008; Ashley et al. 2012). Current

therapeutic approaches involve the use of several commercially available anti-inflammatory drugs or monoclonal antibodies against proinflammatory mediators such as TNF-α, COX-2, and IL-6 to combat inflammation (Schett and Neurath 2018; Zhao et al. 2021; Lima et al. 2022). Although these current approaches are effective, they often suppress the physiological immune responses and thereby complicating the situation and ultimately increasing the infection risk (Schett and Neurath 2018). Recent studies showed that these current strategies failed to provide a definitive therapeutic solution in patients having genetic deficiencies in primary components of inflammation (Perretti et al. 2017; Adhikari et al. 2019). As an alternative, the concepts and mechanisms of the resolution could be a new approach for combating these chronic inflammatory diseases, that not only control the diseases but also revert the course of chronic inflammatory diseases.

2. RESOLUTION OF INFLAMMATION

2.1. Key aspects of Resolution

Inflammation is characterized by two sequential events starting with an initiation phase, which elevates the level of inflammation and is followed by a phase of resolution. The detection of various exogenous and endogenous injurious stimuli, such as viruses, bacteria, oxidants, and aero-allergens, triggers an inflammatory response that is described by the discharge of inflammatory mediators. This phase of inflammation is crucial in effective host defense (Netea et al. 2017). The resolution phase in inflammation process is important to reduce inflammatory response and return tissue homeostasis, thereby preventing the onset of chronic disease (Buckley et al. 2014). Failure to resolve inflammation may result in irreversible tissue damage which increases the risk for developing severe chronic inflammatory disorders like diabetes, asthma, arthritis, colitis, cardiovascular disease, and cancer (Serhan et al. 2011; McInnes and Schett 2017) (**Fig. 1**).

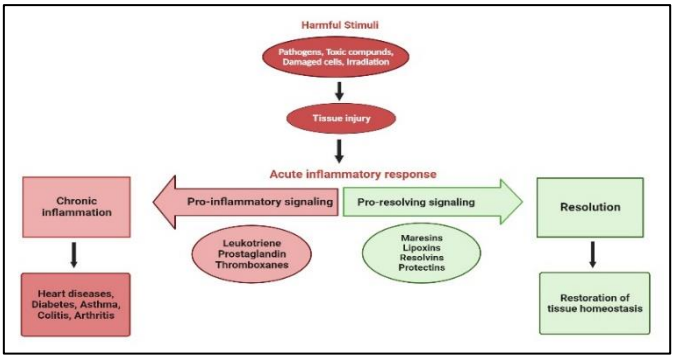

Fig. 1: Role of lipid mediators in the development and resolution of inflammation in Chronic arthritic diseases.

Resolution of inflammation mediates its functions at 3 different levels: molecular, cellular, and macroscopic. Pro-inflammatory mediators are successfully inhibited and metabolized at the molecular level; and immune cell counts at the site of inflammation decrease at the cellular level; and the tissue-repair process is activated to restore tissue integrity at the macroscopic level (Serhan and Savill 2005). The mechanism of effective inflammation resolution is mainly mediated by the specific pro-resolving lipid mediators (SPMs) that regulate the process of resolution (Serhan et al. 2015). However, in the induction phase of inflammation, lipid (e.g., Resolvins, Lipoxins, Protectins, Maresins) as well as protein (e.g., Annexins, D6) mediators, can effectively influence the resolution of inflammation (Serhan et al. 2015; Schett and Neurath 2018). The universal principles of the resolution process are well known, which now embarks on novel approaches for treating inflammatory diseases based on endogenous agonists of resolution.

2.2. Mechanisms of resolution of inflammation

Three essential mechanisms make up the universal mechanism of the resolution, and they work in a variety of tissues and diseases. These processes are:

2.2.1. Cessation of neutrophil influx

Important cellular components such as eosinophils and polymorphonuclear neutrophils (PMNs) travel to the infected regions in response to any injury or infection in order to neutralize and remove such harmful stimuli. This neutrophil spilling over to sites of injury serves as the first step in inflammation pathway (Lämmermann et al. 2013). Since neutrophils are the most prevalent type of leukocytes at inflammatory sites, stalling their recruitment is essential to the resolution step of inflammation. This process is controlled by the pro-resolving lipid mediators (e.g., resolvins). The onset of resolution begins with a class-switch from the pro-inflammatory mediators such as LTB4 and PGE2 to pro-resolving lipid mediators like Prostaglandin D2, Protectin D1, Resolvin E1 (RvE1), Lipoxin A4 (LXA4), and Maresin-1 (Levy et al. 2001). These mediators down-regulate the chemokine receptors like CXCR2, thereby, making the immune cells unresponsive to neutrophil-activating components like leukotriene B4, KC, and complement factor 5 which results in blocking the neutrophil recruitment **(Fig. 2)** (Sogawa et al. 2011). The assembly of pro-resolving lipid mediators was catalyzed by the Arachidonate lipoxygenases (ALOX) and these enzymes have been highly expressed in various cell types like eosinophils, activated macrophages, and specific tissue-resident macrophages

that are involved in the resolution method (Uderhardt et al. 2017).

2.2.2. Neutrophil death and removal

Having a brief half-life, neutrophils are immune cells that have undergone terminal differentiation. Neutrophil apoptosis and its removal are the most vital steps for resolution. As a result, most of the neutrophils die within the target tissue. When macrophages express specific death ligands, such as FasL or TRAIL, through the resolution phase of inflammation, it frequently causes neutrophils to die. (McGrath et al. 2011). These apoptotic neutrophils upon their death are quickly absorbed by pro-resolving macrophages by a process called efferocytosis **(Fig. 2)**. The death and removal a neutrophils by macrophages serve as an essential anti-inflammatory and pro-resolving signal (Huynh et al. 2002).

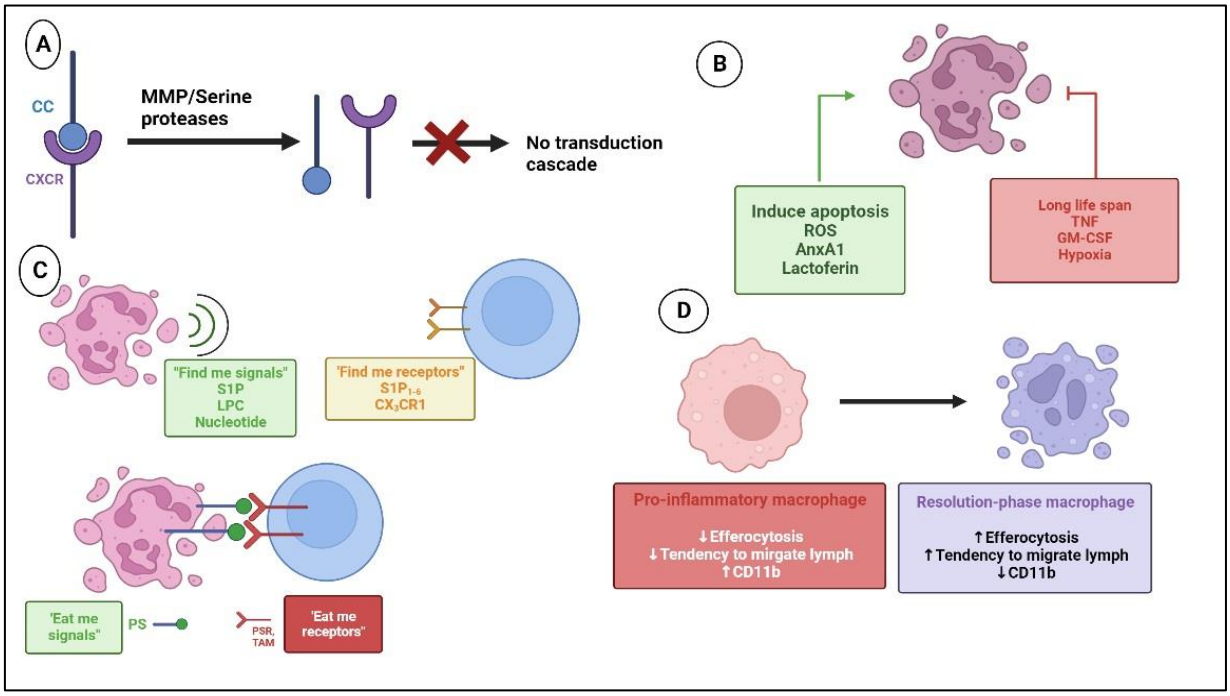

Fig. 2: Mechanism of resolution of inflammation.
A: Chemokines depletion during resolution: CC and CXC chemokines are cleaved by MMPs/serine proteases, rendering them inactive;
B: Neutrophil apoptosis: Factors controlling life span of neutrophil;
C: Clearance of apoptotic neutrophil: The 'find me' signals such as nucleotides, S1P and LPC are secreted by the apoptotic neutrophil, thereby attracting the scavengers. The scavengers then identify the apoptotic cells via the 'eat me' signals exposed on their cell surface, which then triggers the apoptotic cells to be cleared;
D: Macrophage switching: Upon release of local mediators and efferocytosis, the pro-inflammatory macrophages switches to the resolution-phase macrophage resulting in the release of more pro-resolving lipid mediators.

2.2.3. Enrichment of efferocytosis and macrophage reprogramming

Effective resolution of inflammation depends upon the coordinated function between limiting neutrophil recruitment and removal of the apoptotic neutrophils from the site of inflammation. The apoptotic cells are cleared from the body with the help of phagocytes by a process known as efferocytosis. Activated macrophage appears to be essential in this cell clearance event as they remove apoptotic cells and wherein often release pro-resolving lipid mediators (Hannemann et al. 2017). In addition, the active macrophages produce higher amounts of immune regulating intracellular messengers like cAMP and express a variety of anti-inflammatory receptors, including TGF-R2 and FPR2 (Varga et al. 2016). The apoptotic neutrophils enhance the production and expression of "eat-me" "find-me" signals in the form of phospholipids, nucleotides, and phosphatidylserine (PtdSer). These signals are identified by surface-specific receptors like TIM1 and TIM4, of resident macrophages, thereby enhancing the clearance rate by the efferocytes (Li et al. 2003; Kobayashi et al. 2007).

SPMs including resolving (Rv) E1, protectin D1, maresin are released by macrophages that have

engulfed apoptotic cells, thereby contributes in the termination the inflammatory process (Schwab et al. 2007; Serhan et al. 2012). Efferocytosis is therefore necessary for both the removal of apoptotic neutrophils and the production of anti-inflammatory macrophage, which aids in resolution. Numerous autoimmune disorders and chronic inflammatory disease, for example chronic obstructive pulmonary disease (COPD) (Grabiec and Hussell 2016), asthma (Grabiec et al. 2017), RA (Firestein et al. 1995), have been related to a failure to regulate efferocytosis (**Fig. 2**). Therefore, it indicates that inflammation resolution could also be a key target for therapeutics in chronic inflammatory conditions.

2.3. Lipid mediators of resolution of inflammation

The primary aim of inflammation resolution is the rapid and thorough elimination of leukocytes from the inflamed site and the restoration of tissue homeostasis (Van Dyke and Kornman 2008). In this resolution process, the restoration of tissue homeostasis begins with an acute inflammatory response that elicits the generation of lipid mediators involved in inflammation (prostaglandins, leukotrienes). The active class switch of these mediators (prostaglandins, leukotrienes) leads to the generation of SPMs or immunoresolvents (Van Dyke and Freire 2013). These SPMs are biosynthesized during the acute inflammation resolution phase and include resolvins, protectins, lipoxins, and maresins (Bannenberg and Serhan 2010). While protectins resolvins, and maresins are resulting from dietary fatty acids like ω-3 fatty acids found in fish oil, lipoxins are made from endogenous fatty acids like arachidonic acid. At the tissue level, these specialized lipid mediators mediate and expedite resolution by multifactorial pathways (Van Dyke and Freire 2013). To be an ideal pro-resolving mediator one should possess the following characteristics:

a. Cessation of inflammatory cell recruitment: Resolution critically depends on reducing neutrophil inflow and delivering oxygen radicals and tissue-toxic proteases to the site of inflammation.
b. initiation of neutrophil apoptosis and clearance (efferocytosis): Eliminating apoptotic WBC neutrophils is crucial for two reasons; it causes macrophages to undergo reprogramming and stops the toxic contents of their cytoplasm from spilling out when the neutrophils become necrotic.
c. Withdrawal of immune cellular components: The macrophages and dendritic cells go away the site of the inflammation following efferocytosis.
d. Positive immune response modulation: Involves mediating suppressive immune cells and, in turn, the adaptive immune response to deal with subsequent encounter.
e. initiation of tissue repair: The final step of resolution marks the return of tissue homeostasis and no fibrosis or scar formation (Ortega-Gómez et al. 2013).

Some of the prominent pro-resolving mediators are as follows **(Table 1)**:

Table 1. Lipid Mediators of Inflammatory Resolution and their functions

Mediator	Receptor	Pro-resolution functions
Lipoxins A4 and B4	GPR32 and FPR2	• Prevents movement of granulocyte; • Scavenging of cytokines; • Efferocytosis; • Polarization of anti-inflammatory macrophages.
Resolvin E1 (RvE1)	BLT1 and CMKLR1	• Prevents movement of granulocyte; • Downregulate proinflammatory signaling; • Efferocytosis; • Polarization of anti-inflammatory macrophages.
RvD1	FPR2 and GPR32	• Prevents movement of granulocyte; • Downregulate proinflammatory signaling; • Efferocytosis; • Polarization of anti-inflammatory macrophages.
RvD2	GPR18	• Prevents movement of granulocyte; • Efferocytosis.
Protectin D1		• Prevents movement of granulocyte; • Efferocytosis.
Maresins		• Prevents movement of granulocyte; • Efferocytosis.
PGD2	DP1 and DP2	• Prevents movement of granulocyte.

a. Lipoxins

Natural pro-resolving chemicals called lipoxins are produced from endogenous fatty acids. They are a byproduct of the cyclooxygenase (Cox) mediated process that produces arachidonic acid. Lipoxins have potent anti-inflammatory and pro-resolving actions (Serhan et al. 2000). Both Lipoxins A4 and B4 function as inhibitors of polymorphonuclear neutrophil infiltration and act as stimulators of non-phlogistic recruitment of macrophages (Bannenberg et al., 2004).

b. Resolvins

Lipid mediators known as resolvins are biosynthesized from vital ω-3 polyunsaturated fatty acids, for example docosahexaenoic acid and eicosapentaenoic acid. Both of them are obtained from a supplementary derived diet in the form of dietary polyunsaturated fatty acids (PUFA), i.e., eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Bannenberg et al., 2005). Two members of the resolvin family - the D-series, which is formed from docosahexaenoic acid, and the E-series, which is derived from eicosapentaenoic acid - have different chemical structures. The enzyme required for E-series is lipoxygenase (LOX) and for D-series is Cytochrome P450 (CYP). Resolvins play a pivotal role in the resolution of inflammation, including the prevention of neutrophil penetration, efferocytosis, and increasing the clearance of inflammation within the lesion to promote tissue regeneration (Bannenberg et al. 2005).

c. Protectins

Protectins are lipid mediators that are biosynthesized via a lipoxygenase-mediated pathway. This pathway converts docosahexaenoic acid into 10,17-dihydroxydocosahexaenoic acid, known as Protectin D1 (Serhan et al. 2006). It is also known as neuroprotectin and its name stands for the protective actions observed in neural tissues (Mukherjee et al. 2004) and within the immune system (Van Dyke and Freire 2013). Protectin D1 inhibits T-cell migration, increases T-cell death, and decreases TNF-alpha and IFN-gamma release. Protectins decrease polymorphonuclear neutrophil infiltration through endothelial cells and promote the efferocytosis of apoptotic neutrophils (Anderson and Delgado 2008).

d. Maresins

Macrophage mediators in resolving inflammation (maresins) are generated by macrophages by the 14-lipoxygenase pathway. This pathway converts docosahexaenoic acid into 14-H(p)docosahexaenoic acid which is rapidly converted into bioactive products by macrophages (Serhan et al. 2009). Maresin-1 effectively induces efferocytosis of apoptotic neutrophils and also lowers neutrophil numbers in exudate (Serhan et al. 2009).

3. ANTI-INFLAMMATORY VS PRO-RESOLVING THERAPIES

Current anti-inflammatory therapy usually targets controlling the symptoms of inflammation. Most of them block or antagonize key pro-inflammatory mediator pathways that are activated due to the initiation of an acute inflammatory response (Schett and Neurath 2018). Thus, most anti-inflammatory drug function by blocking key biochemical pathways or signaling cascade of key pro-inflammatory mechanisms. However, emerging literature in the past few years has suggested that targeting the infiltrating immune cells by pro-resolving therapy can control the inflammatory response more efficiently (Perretti et al. 2017; Adhikari et al. 2019). Although it does not lead to permanent resolution, it seems to play a pivotal role in combating inflammation. At the moment, anti-inflammatory treatments focus on chemical mediators produced during the resolution phase. These mediators function as an activator in the form of receptor agonists in resolution therapies, which can activate protective mechanisms that result in tissue homeostasis (Perretti 1997; Serhan et al. 2004). So, the new drugs are specifically designed in such a way that can promote both pro-resolving as well as anti-inflammatory functions. Hence, these new pro-resolving drugs would serve as a better option for combating inflammation. Some of the pro-resolving drugs used in the experimental model are listed in **Table 2**. These *in vivo* experimental model studies highlight the role of primary SPMs like AnxA1, resolvins, and LXA4 in the resolution of various inflammatory-related complications. For instance, in a rat model of zymosan-induced arthritis, treatment with LXA4 mediate the resolution process by decreasing the neutrophil infiltration and downregulating the mRNA expression levels of LTB4, CXCL1, and TNFα (Conte et al. 2010). Similarly, lipoxinA4 analogue or nanoparticles containing aspirin-triggered RvD1 can also trigger the

reduction of neutrophil influx into the peritoneum, thereby resolving the peritonitis in mice model (Norling and Serhan 2010).

Table 2: **Pro-resolving drugs and their function**

Disease model (mice)	Drugs	Effect on resolution	References
Rheumatoid arthritis	LXA4	Reduction of oedema, neutrophil inflow, and mRNA expression levels of LTB4, CXCL1, and TNFα	(Conte et al., 2010)
Peritonitis	LipoxinA4 analogue or nanoparticles containing aspirin-triggered RvD1	Reduced neutrophil infiltration into the peritoneum, and intervals of resolution	(Norling & Serhan, 2010)
Peritoneal and lung inflammation	PS/PC liposomes	Stimulate TGF-b secretion, resulting in elevated resolution of inflammation	
Colitis	RvE1	Reducing leukocyte infiltration and pro-inflammatory gene expression, increased survival rates, improvement of histologic scores, sustained body weight	(Arita et al., 2005)
Microbial peritonitis	RvD1, RvD5, PD1s	Efferocytosis of neutrophil and elevated resolution in combination with antibiotics	(Chiang et al., 2012)

4. ROLE OF NATURAL BIO-ACTIVE COMPOUNDS IN THE RESOLUTION OF INFLAMMATION

Chronic inflammatory diseases result from the excessive expression of pro-inflammatory mediators and failure to resolve the inflammatory responses. Recent studies on plant extract and herbal products have shown that plant-based bio-active phytocompounds can directly act on the transcription of the pro-inflammatory mediators. The crude *Aloe vera* gel homogenate was found to be effective in ameliorating chronic arthritis in the Wistar albino rat models by downregulating the expression of various pro-inflammatory markers and cytokines like Cox-2, TNFα (Paul et al. 2021). The methanolic *Drynaria quercifolia* rhizome extract has 7 bio-active compounds that were found to have anti-inflammatory properties. All these compounds showed high binding properties against various pro-inflammatory markers and cytokines like Cox-2, TNFα, and IL-6, and may synergistically show the inhibitory effects on these pro-inflammatory mediators leading to reducing the inflammatory responses by inhibiting the prostaglandin synthesis (Modak et al. 2021). Poly-herbal formulations like Kashayams were also found to inhibit the elevated activities of Cox-2, TNF-α, iNOS, and 5-LOX in the arthritic rat models (Aswathy et al. 2021). The entire plant of *Equisetum diffusum* has been reported to be used by the Mulam people of Guangxi, China for its anti-inflammatory property (Hu et al. 2020). Although these current plant-based approaches are effective they fail to provide a 'total therapeutic solution'. As a result, the use of lipid mediators (SPMs) has increased nowadays, which can mediate both the initiation and resolution of inflammation. The class switching from pro-inflammatory to pro-resolving lipid mediator is considered to be an as efficient alternative strategy to tackle various chronic inflammatory diseases. In this context, plant-based lipid mediators emerge as an alternative option alongside the standard SPMs. A recent study has identified an isomer of the biflavonoid 8-methylsocotrin-40-ol from *Dracaena cambodiana*, a Vietnamese medical plant, which can limit the inflammatory response by targeting 5- lipoxygenase and also triggers the switching of leukotrienes to specialized pro-resolving mediators (SPM), which was evident from the *in vivo* mouse peritonitis model (Van Anh et al. 2021).

5. CONCLUDING REMARKS AND FUTURE PERSPECTIVE

It is certain that, in the near future, more cellular and molecular approaches to the inflammatory response and its subsequent resolution will be discovered. There is also a ray of hope from the clinical trials that modified pro-resolving mediators, and their mimetics are going to be useful in the resolution of inflammation and also in resolving pain, both peripherally and centrally. The use of plant-based

lipid mediators also emerges as a promising candidate found to be effective in controlling the resolution of inflammation. So, the scientific community is in the search of finding this plant-based biflavonoid that will help to provide a 'total therapeutic solution' that not only can control the diseases but also revert the courses of chronic inflammatory diseases. So, the scientific community is searching for these plant-based mediators from different medicinal plants. Since most of the mediators are precursors of either endogenous or dietary fatty acids, some steps also need to be taken on the minimum daily amount of PUFAs (including the ω-3- and arachidonate-derived precursors, both having n-6 and n-3) for timely resolution of inflammatory stress. It is also possible to prescribe the precise amounts of essential PUFAs needed by each individual depending upon his/her gender and age. Nonetheless, nutraceuticals, like PUFA derivatives, can also be prescribed either alone or with some specific pro-resolving mediators such as lipoxin, maresin, protectin, resolvin, and/or combined with other classical anti-inflammatories, e.g., NSAIDs, DMARDs, steroids, etc. It was also found that the designer resolvins could also be used alone or in combination with other anti-inflammatory or pro-resolving therapies. There is also a growing constraint on the synergistic use of various pro-resolving mediators, controlling the resolution of inflammation which may also be effective in the near future. Recent studies also suggest that overexpression of a receptor for a pro-resolving mediator may enhance resolution and that leads to shortening the time of resolution and restoration of the tissue to homeostasis.

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DECLARATIONS

Conflict of interest

The authors declare that there are no conflicts of interest.

Authors contributions

SB conceptualized the idea behind this review manuscript. SS prepared and revised the draft manuscript. Critical revision of the manuscript and approval of the final manuscript was done by SB. Both authors read and approved the final manuscript.

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