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REVIEW ARTICLE

Modulation of Inflammatory Response to Implanted Biomaterials Using Natural Compounds

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Abstract: Tissue engineering offers a promising strategy to restore injuries resulting from trauma, infection, tumor resection, or other diseases. In spite of significant progress, the field faces a significant bottleneck; the critical need to understand and exploit the interdependencies of tissue healing, angiogenesis, and inflammation. Inherently, the balance of these interacting processes is affected by a number of injury site conditions that represent a departure from physiological environment, including reduced pH, increased concentration of free radicals, hypoglycemia, and hypoxia. Efforts to harness the potential of immune response as a therapeutic strategy to promote tissue repair have led to the identification of natural compounds with significant anti-inflammatory properties. This article provides a concise review of the body's inflammatory response to biomaterials and describes the role of oxygen as a physiological cue in this process. We proceed to highlight the potential of natural compounds to mediate inflammatory response and improve host-graft integration. Herein, we discuss the use of natural compounds to map signaling molecules and checkpoints that regulate the cross-linkage of immune response and skeletal repair.

Keywords: Inflammatory response, biomaterials, angiogenesis, tissue engineering, macrophages, natural compounds.

1. INTRODUCTION

The field of tissue engineering has utilized biocompatible materials to synthesize scaffolds with optimal chemical and mechanical properties, in addition to low-level cytotoxicity [1-4]. However, these efforts have been confounded by the host reaction after implantation. Most implanted biomaterials trigger an initial inflammatory response due to the host tissue reaction [5]. Inflammation is the body's response to injury or foreign materials, and is present in numerous diseases, such as rheumatoid arthritis, infection, and cancer [6-8]. As demonstrated in Figure **1A**, following the implantation of a material, the wound healing process begins with the recruitment of neutrophils (polimorphonuclear leukocytes) to the injured site to remove bacteria and foreign bodies by phagocytosis [9-11]. To accelerate the phagocytosis process, neutrophils generate reactive oxygen species (ROS) which sometimes can cause tissue damage [11, 12]. These cells are responsible for producing inflammatory mediators that later recruit and differentiate monocyte to M0 macrophages followed by polarization to M1 pro-inflammatory and M2 pro-healing macrophages. (Figure **1B**). If the host integration is not properly orchestrated, chronic inflammation, inadequate angiogenesis, and biomaterial/device fibrous encapsulation can lead to transplant failure (Figure **1C**). Therefore, for tissue engineering strategies to be successful, it is vital to control biomaterial-host tissue processes interaction [2, 13, 14]. This requires a thorough understanding of the mechanisms by which physiological cues regulate the interaction of inflammatory cells to biomaterials [13-15].

Inflammatory response progresses through adherence of macrophages to implanted materials secreting growth factors, such as fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), cytokines, including tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), granulocyte-colony stimulating factor (G-CSF), and granulocyte macrophage colony stimulating factor (GM-CSF) [16-18]. If acute inflammation is not resolved, biomaterial adherent M1 macrophages will begin to form foreign body giant cells, and the acute inflammation becomes chronic inflammation [18].

It is generally believed that three types of macrophages (M0, M1, and M2) are involved during different phases of wound healing [19]. These macrophages can be polarized by cytokines to differentiate from one phenotype to another [2]. M1 macrophages (pro-inflammatory) are present in the early stage of inflammation and are activated by foreign agents, such as microbes, necrosis, and/or tissue injury [13, 17]. It is hypothesized that M1 macrophages are subsequently differentiated to M2 macrophages (anti-inflammatory) to continue the wound-healing process [20, 21]. M1 macrophages express a number of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, IL-12, and IL-23, as well as chemokines such as CXC ligand motif 2 (CXL2), -9, -10, -11, -12, CC-motif ligand 2 (CCL2), -3, -4, and -5, and inducible nitric oxide synthase (iNOS) [22]. In contrast, M2 macrophages express anti-inflammatory agents including IL-10, along with scavenger, mannose, and galactose receptors [23]. There are multiple sub-types of M2 macrophages, which are distinguished from each other according to their function: M2a macrophages (alternatively activated macrophages) are activated by IL-4, whereas M2c macrophages (activated regulatory macrophages) are activated by immune complexes, glucocorticoids, prostaglandins, and IL-10 [24-26].

Inflammation is mediated by various enzymes; amongst which, the cyclo-oxygenase (COX) is the most extensively studied. COX-1 and COX-2 play critical roles during the transformation of arachidonic acid in prostaglandins [27, 28]. The overexpression of COX2 and prostaglandin is generated by several pro-inflammatory mediators, such as IL-1, IL-6, and TNF-α, and is related to fibrosis encapsulation, scar formation, and delayed wound healing [29, 30]. Due to its role, COX2 has been used in drug discovey studies aimed at the modulation of inflammation. Currently, there are different non-steroidal anti-inflammatory drugs such as celecoxib and indometha-

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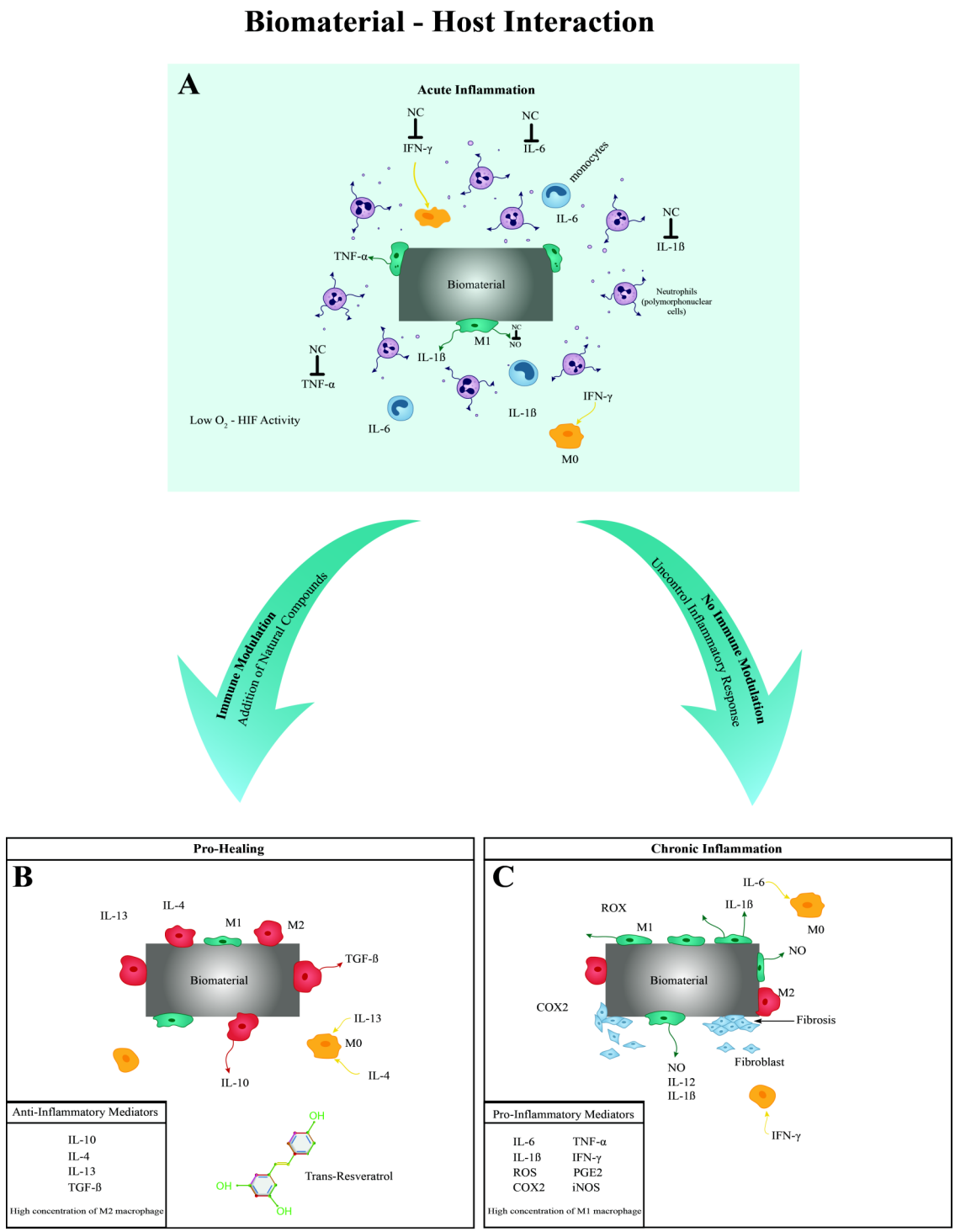

Fig. (1). Biomaterial host interaction. A) Host reaction after biomaterial implantation where neutrophils migrate to the wound site, and monocytes differentiate into M1 macrophages (acute inflammation). Hypoxia can trigger the expression of pro-inflammatory cytokines helping the transition from M1 to M2 macrophages. B) Pro-healing, normal wound healing process where monocytes are polarized to M2 macrophages. The addition on natural compounds (NC) help to improve the inflammation process when they target pro-inflammatory mediators including IFN-γ, IL-6, TNF-α, and IL-1β. C) Chronic inflammation, normal inflammatory respond fails, and pro-inflammatory mediators are over express. M0 macrophages are polarized to M1 macrophages and fibroblast migrate to the device generating fibrosis.

cin that block COX2 and create an anti-inflammatory effect [31, 32]. In addition to this, other natural compounds, such as flavonoids, have been tested to reduce cytokine production and inhibit COX2 overproduction [28].

Inflammation is associated with a number of conditions that represent a departure from physiological environment, including reduced pH, an increased concentration of free radicals, hypoglycemia, and hypoxia. The relationship between oxygen partial pres-

sure and inflammation is difficult to characterize due to the complex interplay of numerous signaling pathways. A departure from physiological oxygen tension in either direction (hypoxia or hyperoxia) can alter gene expression and impact cellular behavior with the consequences of initiating or augmenting inflammation. Additional information regarding the impact of hyperoxia on inflammation can be found in a number of recent reviews [33, 34]. In the context of tissue repair, reduced oxygen levels are more relevant due to the damage to the vasculature at an injury site. In addition, because the establishment of a mature vascular network that can return the local oxygen tension to physiological levels is a process that takes weeks, the impact of the hypoxic conditions on the inflammatory response will be chronic rather than acute.

Alterations in local oxygen tension can be translated into a change in cell phenotype through numerous mechanisms, but the hypoxia-inducible factor (HIF) family of transcription factors is often referred to as the master regulator of this process [35, 36]. HIFs are heterodimers formed between oxygen-sensitive alpha subunits (HIF-1α and HIF-2α) and a constitutively expressed beta subunit (HIF-1β, also referred to as ARNT). HIF-1α degradation is tied to cellular oxygen tension. As the oxygen levels drop below 6% (~47 mm Hg), HIF-1α expression increases and its proteasomal degradation decreases. This change allows dimerization with the beta subunit, interaction with the coactivator CREB-binding protein, and regulation of the transcription of genes with hypoxia-responsive elements in their promoter regions [37].

HIF activity impacts immune cell phenotypes by triggering the expression of IL-1, IL-6, iNOS, TNF-α, and a host of other pro-inflammatory cytokines. Regulatory T cells (T_{reg}) require HIF activity for function, but when HIF activity is elevated by genetic modification, the T_{reg} function in a colitis model is impaired [38]. Similarly, HIF activity is essential for cytotoxic T lymphocytes (CTL) [39]. HIF activity mediates their elevated glycolysis, differentiation, and enhanced granzyme B levels. These results indicate that any perturbation from baseline activity can initiate a cascade with wide-ranging consequences.

The impacts of hypoxia and elevated HIF activity on the phenotypes of macrophages are complex due to the interplay of numerous pathways. Conclusions regarding the impact of hypoxia on macrophage polarity remain somewhat muddled. While oxygen levels can be manipulated easily outside the body, hypoxia is often accompanied by reduced pH, increased concentrations of free radicals, and hypoglycemia *in vivo*. Hypoxia is also used to describe a wide range of oxygen levels; it is expected that macrophages, like other cell types, will show different behaviors in 5, 1 and 0.1% oxygen environments, which is further complicating the goal of reaching consensus [40]. The majority of studies have indicated that hypoxia and HIF activity promote the M1 to M2 transition, which has been summarized in previous review articles [41, 42]. Macrophages have the capacity to switch to anaerobic respiration in low-oxygen environments. In a study that investigated glioblastoma multiforme, hypoxic conditions led to elevated macrophage migration and differentiation of both M0 and M1 macrophages to the M2 phenotype, as indicated by iNOS and arginase 1 (Arg1) staining [41]. A study of intermittent hypoxia (IH) found that resveratrol could reduce the macrophage migration triggered by low oxygen [43]. It is worth noting that this study also showed a shift in the macrophage phenotype towards the M1 form, although this shift could have been the result of differences between IH and chronic hypoxia.

Reactive oxygen species (ROS) are generated as part of the inflammatory response and levels are altered depending on local oxygen tension [44, 45]. ROS can react with, and alter, essential macromolecules in cells such as proteins and nucleic acids. While generation of ROS is the result of oxidative phosphorylation, and therefore occurring in mitochondria of healthy cells, departures from physiological levels can overwhelm antioxidant capacity. This can cause loss of cells, and in turn impaired organ function, due to apoptosis or even initiate oncogenesis.

Hyperoxia can elevate levels of ROS, and this has been studied in neonatal infants placed in high oxygen incubators and in the epithelial lining of the lung during hyperoxia [46]. Such conditions are less relevant in the immediate vicinity of implanted biomaterials. Hypoxia is also linked with ROS generation, in which mitochondrial function plays an essential role. Numerous studies have shown the necessity of mitochondrial activity for ROS-mediated HIF-1a stabilization [47, 48]. This causes elevated expression of HIF target genes and a further increase in ROS levels. These studies also identify potential therapeutic targets to reduce the impact of inflammation on HIF stabilization through ROS. A recent review summarizes many of these phenomena [49, 50].

2. CONVENTIONAL SYNTHETIC DRUGS TO SUPPRESS INFLAMMATORY RESPONSE

The interest in effective mitigation of fibrous capsul formation has led to development of steroidal and nonsteroidal classes of anti-inflammatory drugs. In this context, corticosteroids (e.g. dexamethasone) or glucocorticoids are most commonly used in clinical studies to mimic the functions of anti-inflammatory hormones [51]. Recent *in vivo* experiments demonstrated that augmenting poly(lactic-co-glycolic acid) (PLGA) scaffolds with dexamethasone improved bone regeneration and reduced inflammation. However, other studies have found that this improvement was sustained for only 4 days and corticosteroids induced a negative side-effect on bone homeostasis and density as well as metabolic system interference [13, 52].

A number of antibodies and biologic agents (e.g. infliximab, adalimumab, etanercept, golimumab, certolizumab-pegol, anakinra, and tocilizumab, which antagonize IL-1 and IL-6) have been used to treat chronic inflammation by targeting and inhibiting inflammatory cytokines including TNF-α, IL-1, and IL-6. A drawback with the use of these inhibitors is the increased risk of infection associated with orthopedic surgical implantation [52].

Non-steroidal anti-inflammatory drugs (NSAIDs) have also been used to modulate inflammatory response. Examples of such biological agents include ibuprofen, aspirin, naproxen sodium, celecoxib, and COX2 inhibitors. These types of drugs often target the cyclooxygenase enzymes [52].In general, COX inhibitors are responsible for the conversion of arachidonic acid to prostaglandins. However, studies performed in animal models revealed that these medications affect bone healing by reducing the bone mineral density and mechanical strength in the injured area. Despite limited success, NSAIDs provide short-term relief and do not target the real problem causing the inflammation. [51, 53].

3. NATURAL ANTI-INFLAMMATORY COMPOUNDS TO MODULATE INFLAMMATORY RESPONSE

Over the years, natural supplements have been commonly used to improve health and to reduce effects associated with aging. Natural products can serve as multi-target drugs and thereby improve more than one health problem. These supplements are extracted from various plants, fruits, and herbs and have been used for many years as remedies. Lately, these types of compounds are becoming more popular in modern medicine due to their ability to block or activate multiple pathways. These extracts include flavonoids, triterpenes, and polyphenols, to name a few. In the following, we provide a brief review of *in vitro* and *in vivo* investigations that used different forms of natural compounds to combat inflammatory diseases.

3.1. Polyphenols

Polyphenols have garnered a great deal of interest due to their ability to reduce arthritic damage through their anti-inflammatory and anti-oxidant properties [54, 55]. Recent *in vitro* and *in vivo*

studies have shown that polyphenols down-regulate pro-inflammatory cytokines, stimulate anti-inflammatory agents, increase forkhead box P3 (Foxp3)-expression in CD4+ regulatory T-cells, and prevent bone loss [56]. In the following, we review the promising application of several polyphenols in studies aimed at modulation of inflammation.

3.1.1. Resveratrol

Resveratrol is a natural polyphenol found in various plants including grapes, nuts, and berries among which the skin of red grapes have the highest concentration [57]. Its chemical structure has two phenolic rings bonded together by a double styrene bond, which is responsible for the isometric *cis*- and *trans*-forms of resveratrol [58]. Resveratrol has attracted much attention over the years for its ability to modulate various pathways associated with cell growth, apoptosis, cancer, and inflammation [59]. In addition, recent studies have demonstrated resveratrol to be effective in anti-aging, anti-oxidant, anti-tumor, anti-platelet aggregation, and anti-atherogenic studies [7, 60-64].

Resveratrol has anti-inflammatory properties due to its inhibitory effect on the expression of mediators including IL-1β, matrix metallopeptidase 13 (MMP-13), and COX2 [13, 60, 62]. The mechanism of action of resveratrol is not completely understood, but current research suggests that resveratrol activates the silent information regulator T1 (SIRT1) protein in the cells which helps to reduce pro-inflammatory cytokines by cutting down nuclear factor kappa B (NF- κB).

The tissue engineering community has utilized resveratrol to modulate inflammatory response to biomaterials. Resveratrol encapsulated in specific scaffolds for local delivery potently down-regulated TNF-α and IL-1β and suppressed COX2 while blocking NF-κB activation [62, 65]. Cellular analysis revealed that resveratrol encapsulated in PLGA nanoparticles reduced the expression of pro-inflammatory agents (IL-6 and TNF-α), whereas it increased the expression of anti-inflammatory genes including IL-10 and vascular endothelial growth factor (VEGF), which promoted osteogenesis as demonstrated by alkaline phosphate (ALP) expression in mesenchymal stem cells (MSC). In a recent discovery, resveratrol-polyacrylic acid particles were utilized in an atelocollagen matrix to enhance cyto-compatibility, proliferation and cell viability of marrow stromal cells. In addition, the authors found that these scaffolds down-regulated IL-1β, COX2, and MMP-13 [65]. The *in vivo* data obtained in a rabbit osteochondral defect model showed that a resveratrol-poly(acrylic acid)-collagen hydrogel increased bone and cartilage gene expression. In another study, Elmali *et al*. evaluated the effect of resveratrol in rabbits with induced arthritis by injecting resveratrol in the affected area. The authors observed that resveratrol decreased the cartilage damage and inflammation [62]. These studies demonstrate the potential of resveratrol to be used as an anti-inflammatory natural molecule which can also enhance tissue integration.

Resveratrol has demonstrated a dose response effect in various clinical, *in vitro*, and *in vivo* studies. While published data have not reported adverse effects of resveratrol in humans, in some animal studies, high dosages (3 g/kg/day in rats) has led to death due to nephrotoxicity [66]. In contrast, several *in vitro* and *in vivo* studies have reported that resveratrol is well-tolerated and relatively non-toxic [67, 68]. Further studies are warranted to elucidate the mechanism of action, as well as the dose response safety, of resveratrol in clinical applications aimed at modulation of inflammation. Another major challenge is the low bioavailability due to rapid and extensive metabolism of resveratrol. Approaches that utilize nanotechnological formulations to control release of resveratrol may help expedite the path of resveratrol to clinical trials.

3.1.2. Curcumin

Curcumin is a polyphenol found in the root of the turmeric plant, *Curcuma longa*. Curcumin exhibits anti-infectious, chemo-preventive, pro-apoptotic, anti-angiogenic, and anti-inflammatory properties [8, 69]. Its anti-oxidant properties are associated with the inhibition of the nitrite-induced oxidation of hemoglobin [70]. The antioxidant effect of curcumin is highly potent due to its multiple functional groups (B-diketo group, carbon–carbon double bonds, and phenyl rings containing various amounts of hydroxyl and methoxy substituents) [71].

The mechanism of action of curcumin during inflammation is related to the suppression of pro-inflammatory pathways (nuclear factor erytroid-2 related factor-1, Nrf2-keap 1, and NF- κB) and the down-regulation of several cytokines including TNF-α, IL-1, IL-6, IL-8, and IL-12 in various cell types [70-75]. Studies performed in rats that were positive for inflammatory markers showed significant suppression of TNF-α, C-reactive protein (CRP), and COX2 [76]. Consistent with these findings, studies performed with colon cancer cells (HT29 and SW480) showed a down-regulation of COX2 and inhibition of prostaglandin-E2 (PEG2) when exposed to curcumin [77]. The *in vivo* studies by Miao *et al*. showed that in rats subjected to an induced middle cerebral artery occlusion, curcumin administration by intraperitoneal injections for 5 days led to TNF-α and IL-6 down-regulation [78]. In addition, the oral administration of curcumin has led to reduced inflammation in patients with ulcerative proctitis and Crohn's disease as well as accelerated wound healing [79].

Curcumin blocks the adhesion of monocytes to endothelial cells which suppresses tumor vascularization, a process essential for tumor metastasis [70]. Clinical research with osteoarthritis patients has shown that a curcumin-phospatidylcholine complex reduces the oxidative stress, down-regulates IL-1β, IL-6, and improves pain and various osteoarthritis symptoms [72]. Another interesting study was conducted by Sun *et al*. to encapsulate the curcumin into exosome nanoparticles in order to increase its solubility and induce lipopolysaccharide (LPS) [8, 69, 79]. Curcumin has been also encapsulated in pH-sensitive nanoparticles to decrease neutrophil infiltration and reduce TNF-α [80].

Although more research is called for, the immune modulatory property of curcumin renders it as an inexpensive, natural choice in tissue engineering applications [81-83]. Nevertheless, its short biological life, low absorption, and fast metabolism have hampered the enthusiasm for its use in clinical applications [84]. In spite of these limitations, further explorations to design novel curcumin formation derivatives to enhance systemic bioavailability and efficacy are needed for future human use.

3.1.3. Green tea (Camellia sinenesis)

Green tea (Camellia sinenesis) contains the major polyphenolic compounds epigallocatechin-3 galate (EGCG) and flavonoids. Evidence in literature suggest that the bioactive compounds of green tea prevent cardiovascular problems, cancer, inflammation, and neurodegenerative problems due to its anti-oxidant and anti-inflammatory properties [85-89]. Several studies have examined the mechanism of action of the green tea components in the improvement of bone formation [25]. *In vitro* studies utilizing cancer cell lines revealed that EGCG induces apoptosis and promotes cell growth arrest by regulating the cell cycle regulatory proteins, activating killer caspases, and down regulating IL-1β and NF-κB [57, 90]. However, cell apoptosis was not observed in healthy cells. Studies performed with osteoblastic cells revealed that green tea increased osteoblast survival and decreased the cell apoptosis due to TNF-α and IL-6 inhibition [91]. Additional findings suggest that EGCG inactivates additional pro-inflammatory agents, such as PEG2, nitric oxide (NO), and COX2 [86]. Consistent with these results, studies performed in rats with induced chronic inflammation demonstrated that the green tea polyphenolic compounds reduced chronic inflammation while preserving the bone mass and microarchitecture [87]. For example, Leong *et al*. found that green tea reduced the expression of pro-inflammatory agents (IL-1β,

TNF-α, and IL-6) and inflammatory cell infiltration in osteoarthritis mouse model [92].

The toxicity of compounds isolated from green tea has been assessed in animal models to determine the lethal dose as well as hematologic and biochemical abnormalities. In one study, it was found that the median lethal dose was above 3-5 g/kg in rats [93]. The modulatory effect of EGCG on bone mineralization and VEGF activation combined with its effect on down-regulation of inflammatory cytokines reaffirms the significant potential of green tea extracts in tissue engineering applications.

3.1.4. Omega 3

Omega 3 is a natural anti-inflammatory compound mainly found in fish oil with active ingredients of eicosapentaenoic acid (EPA), docosahexanoic acid (DHA), and poly-unsaturated fatty acids (PUFAs) [94, 95]. Most of the studies of omega 3 have traditionally focused on cardiovascular diseases, obesity, and diabetes showing the potential of EPA and DHA to augment the production of PEG3 and inhibit the transformation of arachidonic acid to PEG2 [23, 57]. Studies performed in LPS-stimulated mouse microglial cells assessed the mechanism of action of EPA, DHA, and PUFAs. The data demonstrated that these three active ingredients of Omega 3 activate the SIRT1 pathway by inhibiting NF-κB and reducing IL-6 and TNF-α expression [96]. Clinical investigations have revealed that patients who receive an omega 3 treatment demonstrated a suppression in arachidonic acid [97, 98]. In addition, it was shown that omega 6 activates the choline and ethanolamine phosphoglycerides and inhibited NF-κB activation [97, 98]. In another important study, Turnen et al. found that TNF-α and IL-6 expression in serum decreased in patients who were treated with omega 3 [95]. Further evidence was demonstrated in a recent in vitro study showing that PUFA inhibited LPS effect in murine RAW macrophages leading to a reduction in the numbers of M1 macrophages and an increase of M2 macrophages in the adipose tissue in a mouse model [99].

A recent report coming out of Mayo Clinic has provided evidence that omega 3 is not toxic in low and moderate dosages [100]. In contrast, Sijben and Cader revealed that an n-3 PUFA supplement depressed immune system due to an alteration in cytokine production, T-cell proliferation, and T cell-mediated cytotoxicity [101]. In another study, Woodworth et al. pre-treated mice with a 3 g/kg EPA + 32.4 g/kg DHA diet for 6-8 weeks before inducing colitis. The histophatology results revealed that EPA and DHA pre-treated animals had a higher degree of inflammation and rate of mortally as compared to the control group (regular diet enriched with corn oil or safflower oil). These observations can be related to immune system alteration [102].

3.1.5. Proanthocyanidins

Proanthocyanidins are a class of polyphenolic compounds present in the fruits, bark, leaves, and seeds of various plants, which possess anti-bacterial, anti-viral, anti-inflammatory, and vasodilatory properties [26, 103, 104]. The treatment of murine macrophages with a proanthocyanidin has recently been shown to down-regulate a number of inflammatory cytokines including IL-1β, COX2, IL-6, and TNF-α [105]. In addition, *in vivo* studies have revealed that proanthocyanidin augments the expression of IL-4, IL-10, and transforming growth factor β (TGF-β1) while dampening the expression of IL-1β, macrophage inflammatory protein 1 (MIP-1), and monocyte chemoattract protein-1 (MCP-1) in a mouse model of induced arthritis [26, 103].

Proanthocyanidin has a great potential to combat venous and capillary diseases as well as tumor formation due to its anti-thrombotic and anti-inflammatory effects. In a recent study in rats with cardiovascular conditions, the oral administration of oligomeric proanthocyanidin was shown to reduce atherosclerosis [106]. The macrophage differentiation was controlled through down-regulation of vascular cell adhesion protein 1 (VCAM-I) and monocyte chemoattractant protein-1. *In vitro* studies on exposing two types of pancreatic cells (Miapaca-2 and AsPC-1) to proanthocyanadin extract for 48 hour found a significant reduction in NF-κB and IκB kinase-α (IKK-α) in addition to reversal of the epithelial to mesenchymal transition process [107, 108]. Published data utilizing cardiomyocytes have shown that at low concentrations (5-10 μg/ml), proanthocyanidin possesses antioxidant properties, while at high concentrations, (100-500 μg/ml) proanthocyanidin becomes a pro-oxidant compound, inducing ROS production and causing cell death [109].

3.1.6. Uncaria tomentosa

Uncaria tomentosa is a Peruvian woody vine known as cat's claw. The active compounds of this source include diverse arrays of polyphenols. Uncaria tomentosa has been shown to be effective in the treatment of various diseases including rheumatism, irregular menstruation, tumorigenesis, and kidney problems [110, 111]. Several studies have revealed that this natural compound has anti-inflammatory properties on the basis that it inhibits TNF-α expression and NO synthase and suppresses the activation of NF-κB [57, 110]. This observation was consistent with an *in vivo* study demonstrating that an oral dose of Uncaria tomentosa suppressed TNF-α, IL-1α, and IL-1β, IL-4, and IL-17 [111]. Furthermore, the administration of Uncaria tomentosa for 8 days lowered the expression of pro-inflammatory markers including NF-κB, COX1, and COX2 [112-115]. Other studies have shown that Uncaria tomentosa inhibits proliferation of tumor cells without causing cell death and improving cells' DNA repair [116]. Despite its significant potential, the use of uncaria tomentosa at higher doses (320 μg/ml) is not recommended due to cytotoxic effects (blocking cell proliferation) and safety issues [110, 113].

3.2. Flavonoids

Flavonoids are water soluble metabolites abundantly found in plants which have shown many health benefits. They are most famous for their antioxidant, anti-inflammatory, and anti-carcinogenic properties [56, 117]. In the following, we provide a review of four promising flavonoids with potential to mediate inflammatory response to biomaterials.

3.2.1. 6-Shogaol

6-shogaol is one of the main compounds extracted from ginger which has been shown to possess anti-inflammatory, anti-carcinogenic, and anti-oxidant properties due to its inactivation of NF-κB and down-regulation of IL-1β in a mouse model [56, 118-120]. It has been used to treat neurodegenerative diseases such as Alzheimer's and Parkinson's due to its anti-neuroinflammatory and anti-oxidant properties [121]. In a recent study it was found that LPS-induced rat astrocytes treated with 6-shogaol showed an improvement in neuro-inflammation due to reduction in the levels of IL-1β and IL-6, down-regulation of iNOS and COX2, and inactivation of NF-κB pathway [122]. Furthermore, it has been demonstrated that 6-shogaol blocks the expression of iNOS and COX2 and inhibits the transcription of NF-κB in LPS-induced macrophages and in a mouse model [119, 123]. The applicability of this compound is not limited to neuro-inflammation. In fact, 6-shogaol treatment of rats, in which complete Freund's adjuvant (CFA) had been administered to the synovial cavity of the knee, led to a significant reduction in the knee swelling and inflammatory cell infiltration in the affected area [53]. In the context of cancer therapeutics, Shogaol compounds (6-shogaol and 3-phenil-3-shogaol) down-regulated NF-κB and the associated MMP-9 expression in breast cancer cells while suppressing IL-1β and TNF-α in LPS-induced microglia cells [123, 124]. Studies performed using breast cancer cells (MCF-7, dosed with 6-shogaol 39.52 μM), revealed that 6-shoagaol reduces the expression of cancer stem cell markers ($CD44^{+}$, and $CD24^{-/low}$) due to the mitotic block and interference with the self-renewal pathway. Higher concentrations of 6-shoagaol have been shown to be safe for noncancerous cells (HEK 293 and

HaCaT cells treated with 69.97 and 103.84 μM, respectively) [125]. Further *in vivo* studies will be needed to obtain a definitive evaluation of toxic effects and clinical potential of 6-shoagol.

3.2.2. Salicylate (Salycilic Acid or Salicin)

Salicylate (salycilic acid or salicin), the main component of aspirin, is a natural compound extracted from white willow bark which is and has been used to treat pain, inflammation, fever, and recently, osteoarthritis and lower back pain [57, 126, 127]. Salicylate is a non-selective inhibitor of COX1 and COX2 and induces an anti-inflammatory effect in a variety of diseases [127, 128]. A recent *in vitro* study has shown that administration of D(-)-salicin down-regulates TNF-α, IL-1β, and IL-6 in LPS-induced inflammatory macrophages [129]. Consistent with this finding, the intraperitoneal injection of D(-)-salicin reduced TNF-α, IL-1β, and IL-6 levels and significantly increased IL-10 levels in mice with LPS-induced inflammation [129]. In addition, D (-)-salicin was shown to inhibit the infiltration of neutrophils and macrophages into LPS-induced lung tissue, improve the accumulation of nuclear factor erythroid 2-related factor-2 (NRF-2), and reduce oxidative stress [129]. Due to these anti-inflammatory properties, salicylate has been used to treat a number of inflammatory diseases. For example, in a recent study colitis was treated with salicylate by intraperitoneal injection for 7 days leading to suppressed edema, mucosal damage, and gross bleeding [130]. Another relevant application is the development of fully bio-absorbable salicylate-base sirolimus-eluting stent, which was implanted in a porcine coronary artery. The authors reported a positive device incorporation without causing excessive thrombotic reaction [131]. The therapeutic use of salicylate, however, faces challenges due to side effects including gastrointestinal irritation [128, 132, 133]. Studies performed in rats showed evidence that salicylate (10-100 mM) intestinal irritation is due to the intestinal epithelial cell permeability [134]. There have also been isolated reports of toxic side effects associated with the use of salicylates. As such, future investigations should determine the efficacy of low-dose therapies.

3.2.3. Naringin

Naringin is a bioflavonoid mainly found in grapefruits and other citrus fruit. Naringin possesses anti-carcinogenic, anti-oxidant, anti-inflammatory, lipid-lowering, superoxide scavenging, anti-atherogenic, and metal-chelating effects [117, 135]. Recent investigations have revealed that naringin administration suppressed NF-κB activation and inhibited NO production in both LPS-induced macrophages and LPS-induced mice [136, 137]. A number of clinical studies have used naringin to treat inflammatory diseases *in vivo*. For example, using a rat model, investigators have shown that naringin down-regulates TNF-α and NF-κB levels in cis-induced striatal injury [135] and kidney injury (gentamicin nephrotoxicity) [138]. In another study, a two-week treatment with naringin improved swelling, decreased the T-cell numbers, down-regulated IL-17A and IL-1β, increased the Treg population, up-regulated Foxp3 and trans-acting T-cell-specific transcription factor (GATA-3), and activated IL-10 and IL-4 in mice with induced polyarthritis [117]. The oral administration of naringin has also been demonstrated to inhibit NF-κB in bronchoalveolar lavage fluid and reduce neutrophil infiltration into the lungs of LPS-induced acute lung injury as well as suppress MMP-9 expression in paraquat-induced pulmonary fibrosis in mice [139, 140]. Despite the significant benefits of Naringin, this natural compound has shown to cause several side effects including nausea, anorexia, and vomiting due to the inappropriate diffusion in the brain [141].

3.2.4. Quercetin

Quercetin is a polyphenolic flavonoid mainly found in fruits and vegetables. Quercetin possesses anti-oxidant, anti-carcinogenic, anti-inflammatory [142], and mitochondria protective effects [143]. Recent studies have revealed that quercetin administration prevented the increase of inflammatory cytokines including IL-1β, TNF-α, and IFN-γ in addition to suppressing the activation of NF-κB both *in vivo* and *in vitro* [143, 144]. The administration of quercetin induced the activation of nuclear factor NRF2 in LPS-induced human aortic endothelial cells [145]. It has been discovered that NRF2 protects against inflammation by down-regulating pro-inflammatory cytokines [146]. Consistent with this finding, human intestinal biopsies from inflamed areas were treated with quercetin, and the results revealed that quercetin up-regulated secretory leukocyte protease inhibitor (Slpi) expression and suppressed TNF-α [145]. More recent clinical studies revealed that quercetin oral administration of quercetin to patients with rheumatoid arthritis reduced TNF-α levels in plasma [147].

The application of quercetin is hampered by deglycosylation limiting the lifespan of this flavonoid. To overcome this limitation, researchers encapsulated quercetin in poly(L-lactic acid) scaffolds to preserve the antioxidant's stability properties and more effectively deliver the compound [148]. In light of advances in drug delivery approaches and given the striking potential of this herb in modulating inflammation, further studies are warranted to assess its clinical utility in combination with scaffolds in regenerative medicine.

3.3. Triterpenes

Triterpenes are a class of active natural compounds that are found in leaves, stem bark, fruits, and roots which have been the focus of phytochemical investigations. In the following, we review recent in vitro and in vivo studies that used three types of triterpenes to combat inflammatory diseases.

3.3.1. Tinospora cordifolia (Guduchi)

Tinospora cordifolia (Guduchi) belongs to the Menispermaceae family and is found in Southeast Asia. Various active ingredients including alkaloids, steroids, diterpenoids, lactones, aliphatics, and glycosides can be extracted from different parts of this plant [149]. Published data have shown the potential of tinospora cordifolia to treat various diseases due to its anti-diabetic, anti-malarial, anti-oxidant, anti-allergic, and anti-inflammatory properties [24, 149-153]. Diterpenoids, lactones, and aliphatic compounds are responsible for the anti-inflammatory effects of this plant [149]. Tinosfora cordifolia regulates both pro- and anti-inflammatory pathways by the activation of various cytokines [153]. In one study, Sannegowda *et al*. found that when rats with an induced form of arthritis were treated with tinosfora cordifolia extract, it down-regulated several pro-inflammatory cytokines including IL-1β, IL-6, IL-23, TNF-α and MIP-1 [154]. In another recent study, oral delivery of tinosfora cordofila led to significant down-regulation of iNOS, COX2, and intercellular adhesion molecule-1 (ICAM-1) in asthmatic mice [155]. Tinosfora cordofila extract (octacosanol) inhibited tumor cell proliferation and the angiogenesis of Ehrlich tumor cells implanted in mice through inhibition of NF-κB activation [156].

Tinosfora cordifolia extract has shown to be pro-osteogenic. Human osteoblast-like cells and primary rat osteoblastic cells proliferated at a higher rate and accelerated mineral content deposition when exposed to a Tinosfora cordifolia extract [150, 157]. A recent study revealed that osteoblasts enhance mineral deposition when exposed to 12.5-25 μg/ml of tinosfora cordofila. This effect was measured by monitoring alkaline phosphatase and calcium depsotion in rat primary osteoblast as well as human osteoblast-like MG-63 cells in the presence of Tinosfora cordofila [158]. These results all together demonstrate the potential of tinosfora cordofila to be used in tissue engineering applications to concurrently enhance bone repair and alleviate inflammatory response.

3.3.2. Boswellic acid

Boswellic acid is a pentacyclic triperpenoid that is extracted from the resin of the *Boswellia serrata* tree [159]. Boswellic acid is a combination of the triterpenoids β-boswellic acid, 3-acetyl-β-boswellic acid, 11-keto-β-boswellic acid, and 3-acetyl-11-keto-β-

boswellic acid. It has been used to treat chronic inflammation in rheumatoid arthritis, asthma, ulcerative colitis, and Crohn's disease on the basis that it targets NF-κB, signal transducer and activator of transcription 3 (STAT3), androgen receptor (AR), p21, death receptor 5 (DR5), and caspase-3 and -8 [159-161]. It has been reported that this plant has anti-cancer properties due to its capacity to inhibit growth and to induce apoptosis [159, 162]. *In vitro* studies have reported that boswellic acid inhibits iNOS activity in LPS-induced macrophages [163]. Other studies have revealed that boswellic acid suppresses NF-κB and STAT in several cancer cell lines, including HT-29 colon, SW-620, Colo-205, Hep-2 larynx, DU-145 prostate, and PC-3, confirming the anti-cancer activity of boswellic acid [162]. Animal studies have shown that boswellic acid leads to reduction in the weight of the tumor-like cells, inhibition of fibrovascular tissue, and a down-regulation tumor angiogenesis.

Arthritis is another inflammatory disease for which boswellic acid has demonstrated significant therapeutic promise. *In vivo* studies in mice with an induced form of steoarthritis demonstrated significant improvement when treated with boswellic acid for 12 weeks. Safranin-O-staining analysis showed that the boswellic acid treatment reduced the articular cartilage erosion, knee synovitis, and osteophyte formation and inhibited IL-1β and Toll-like receptor 4 (TLR4, an innate immune system activator) in the osteoarthritic synovial explanted tissue [164]. Most recently boswellic acid was declared as a new class of safe and high tolerance NSAID [165].

3.3.3. Celastrol

Celastrol is a compound found in the root of *Tripterygium wilfordii*, which is better known as "Thunder God Vine" [166]. Celastrol has been studied for the treatment of asthma, skin inflammation, arthritis, systemic lupus erythematosus, hypertension, and neurodegenerative disorders [167]. Recent data has shown that celastrol inhibits NF-κB pathway leading to a significant reduction in the expression of IL-6 and IL-1β in myeloid cells [168]. Clinical investigation of this natural compound has identified a number of health benefits including anti-oxidant, anti-cancer, and anti-inflammatory properties [169]. In a recent study, Cascão *et al*. found that celastrol, injected intraperitoneally for 19 days, down-regulated the expression of IL-1β and TNF-α and suppressed NF-κB and caspase-1 activation in rats with adjuvant-induced arthritis [166]. The underlying mechanism for this effect was the ability of celastrol to induce heme oxygenase-1 (HO-1), inhibit the effect of interferon gamma (IFNγ)-induced monocyte adhesion, and down-regulate ICAM-1 [166]. A similar effect on inflammatory cytokine expression in human THP-1 and T cells was noted in other studies [170-172]. Toxicological analysis performed on zebra fish have shown that 1 μM celastrol is toxic for this animal model as a high rate of mortality was observed 48 hours after exposure. In addition, this study revealed that lower concentrations (0.5 μM) generated animal tail malformation [173]. A comprehensive study of Celastrol's pharmacokinetics profile, bioavailability, and toxicological effects in animal models is warranted to expedite its potential move to clinical trials.

CONCLUSION

The emerging insight into the role of inflammation in tissue remodeling has led to a paradigm shift in tissue engineering approaches; rather than seeking means to suppress immune response, current efforts focus on identifying ways to harness the potential of inflammatory cells to encourage vascularization and osteogenecity. The limited success of above strategies in recapitulating the temporal aspects of the crosstalk between various cellular constituents is inherent in the design principle to target a single biological event. Having developed over an evolutionary timescale, complex pathologies such as tissue regeneration embrace a plethora of signaling pathways and inflammatory mediators acting together. The pathogenesis of these biological processes are rather multi-factorial in nature and not due to a single cytokine or cellular phenomenon. The remarkable capability of natural compounds to bind to various sites of multiple interacting molecular targets offers an innovative approach to identify and modulate targets in interdependent biological processes such as inflammation, angiogenesis, and tissue repair. Exploiting the potential of pharmacologically active natural compounds may offer a safe and robust approach to regulate the complex signaling network that governs these pathologies

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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