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Modulation of neutrophil (dys)function by Ayurvedic herbs and its potential influence on SARS-CoV-2 infection

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Running title: Ayurvedic herbs modulating neutrophil functions

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Abstract

For centuries, traditional medicines of Ayurveda have been in use to manage infectious and non-infectious diseases. The key embodiment of traditional medicines is the holistic system of approach in the management of human diseases. SARS-CoV-2 (COVID-19) infection is an ongoing pandemic, which has emerged as the major health threat worldwide and is causing significant stress, morbidity and mortality. Studies from the individuals with SARS-CoV-2 infection has shown significant immune dysregulation and cytokine overproduction. Neutrophilia and neutrophil to lymphocyte ratio has been correlated to poor outcome due to the disease. Neutrophils, component of innate immune system, upon stimulation expel DNA along with histones and granular proteins to form extracellular traps (NETs). Although, these DNA lattices possess beneficial activity in trapping and eliminating pathogens, NETs may also cause adverse effects by inducing immunothrombosis and tissue damage in diseases including Type 2 Diabetes and atherosclerosis. Tissues of SARS-CoV-2 infected subjects showed microthrombi with neutrophil-platelet infiltration and serum showed elevated NETs components, suggesting large involvement and uncontrolled activation of neutrophils leading to pathogenesis and associated organ damage. Hence, traditional Ayurvedic herbs exhibiting anti-inflammatory and antioxidant properties may act in a manner that might prove beneficial in targeting over-functioning of neutrophils and there by promoting normal immune homeostasis. In the present manuscript, we have reviewed and discussed pathological importance of NETs formation in SARS-CoV-2 infections and discuss how various Ayurvedic herbs can be explored to modulate neutrophil function and inhibit NETs formation in the context of a) anti-microbial activity to enhance neutrophil function, b) immunomodulatory effects to maintain neutrophil mediated immune homeostasis and c) to inhibit NETs mediated thrombosis.

Introduction

Coronavirus disease 2019 (COVID-19) by SARS-CoV-2, a plus strand RNA virus, is an ongoing pandemic and is causing respiratory disease associated with pneumonitis. Over the past months, COVID-19 crisis has caused devastating illness globally leading to enormous socio-economic burden. Epidemiological data as on early December , 2020 indicated by world health organization reveals 66,729,375 confirmed cases and 1,535,982 deaths worldwide [1]. Although major sub-group of SARS-CoV-2 infected patients are clinically asymptomatic or minimally symptomatic, approximately 5% patients exhibit significant lung damage and/or multiple organ failure. Critically ill patients infected with SARS-CoV-2 manifest shock, sepsis, localized and systemic coagulopathies and these pathological conditions are significantly associated with acute inflammation [2]. Mechanistically, Angiotensin – Converting Enzyme 2 (ACE2) serves as one of the receptors for SARS-CoV-2 in pulmonary tissues and reduces bioavailability of ACE2 [3]. Decreased ACE2 levels results in the loss of its protective effects by increasing AngII levels, which induces oxidative stress and pro-inflammatory milieu *via* NADPH oxidase [2]. Increasing evidences suggest that the pandemic causes approximately 10–15% of the patients to progress towards acute respiratory distress syndrome (ARDS) [4]. Characteristically, ARDS shows elevated inflammation in pulmonary tissues, thick mucous secretions in the airways, increased levels of systemic pro-inflammatory cytokines and extensive lung damage. Taken together, pathogenesis of SARS-CoV-2 comprises bidirectional activation of inflammatory and oxidative stress pathways involving innate immune cells such as neutrophils.

Neutrophil extracellular traps in health and disease

Neutrophils are one of the critical constituents of innate immune system and play a significant role in fighting infections using range of arsenal of antimicrobial functions. Neutrophils belonging to granulocyte lineage of white blood cells, acts as the first line of defence against pathogens and eliminate them by a) degranulation, b) phagocytosis and c) by producing extracellular traps. Upon stimulation, neutrophils expel their DNA along with histones and granular proteins to form extracellular traps through a process referred as NETosis. Existence of NETs were discovered by Brinkmann *et al.* (2004) and showed these entities were composed of DNA lattices which trap and eliminate bacteria [5]. NETs are the scaffolds of decondensed chromatin and may contain both nuclear and mitochondrial DNA [6]. Subsequent analysis revealed NETs contained high concentrations of antimicrobial

effectors including variety of proteases, histone variants and anti-bacterial peptides and these may aid in clearing the infection [7]. NETs participate as a defensive action against a broad range of microorganisms including viruses, bacteria, fungi and protozoa [8].

Variety of viruses have been demonstrated to activate pattern recognition receptors (PPR) in neutrophils to induce NETs formation and more interestingly, signalling effector mediators of virus induced NETs differed from that of bacteria. Upon binding to viral DNA, human immune deficiency virus (HIV-1) induced formation of NETs through endosomal PRR, TLR-7 and TLR-8 [9]. Respiratory syncytial virus fusion protein induced NETs activating TLR-4 [10]. Hantavirus has been demonstrated to form NETs *via* β2 integrin signalling in human neutrophils [11]. Narayan Moorthy *et al.* (2013) showed influenza A virus induced NETosis and however these NETs failed to protect against secondary bacterial infection of Pneumococcus [12]. However, virus induced NETs have been shown to act as double edged sword as they possess anti-viral activity and also induce organ damage during viral infections [13].

Neutrophil response in COVID-19 infections

Pulmonary inflammation during SARS-CoV-2 infection is characterized by the dysregulated innate immune system function associated with neutrophilia, infiltration of neutrophils and increased levels of pro-inflammatory mediators. Haematological analysis of 452 SARS-CoV-2 infected subjects in Wuhan, China, showed dysregulated immune response with lower lymphocytes counts, increased leukocyte counts and neutrophil-lymphocyte-ratios, (NLR), decreased percentages of monocytes, eosinophils, basophils and both T helper and suppressor cells [14]. Recent meta-analysis of 15 studies constituting 3090 SARS-CoV-2 infected individuals indicated high neutrophil count and NLR significantly correlated with severity of the disease [15]. Wang *et al.* (2020) in a retrospective study of 139 hospitalized subjects suggested correlation of neutrophilia to poor outcome [16]. Autopsy samples from different studies reported infiltration of neutrophils in pulmonary capillaries along with fibrin deposition, neutrophils extravasation into the alveolar space, and neutrophilic mucositis [4,17]. Taken together, accumulating evidence suggest over functioning of neutrophils in advanced stages of COVID-19 associated ARDS. Neutrophils, component of innate immune system, combats pathogens by expelling DNA outside along with histones and granular proteins, and produce extracellular traps (NETs). Although NETs show beneficial effects, these DNA lattices also possess adverse effects on variety of diseases such as diabetes and

atherosclerosis where, the NETs induce thrombosis and tissue/organ damage [18]. Interestingly, SARS-CoV-2 infected subjects with co-morbid conditions such as diabetes and atherosclerosis are more prone to mortality. Along with pro-inflammatory parameters, abnormal conditions such as disseminated intravascular coagulation [19], altered conventional coagulation parameters [20] and increase in the thrombus formation under hypoxic conditions [21] are observed in SARS-CoV-2 subjects and these can also be due to the cause or consequences of NETs formation. Neutrophils greatly outnumber other blood mononuclear cells at the site of infection and inflammation can produce reactive oxygen species as well as can release several pro- and anti-inflammatory mediators. Zuo *et al.* (2020) analysed sera of 50 COVID-19 infected individuals and showed elevated NETs components as an indication of hyper-activation of NETs [22]. Hence, targeting neutrophil functions, more specifically NETs formation, during SARS- CoV-2 infections might be beneficial in reducing the morbidities in advanced stages.

NETs in respiratory diseases/infections

Over the years, several studies have demonstrated dysregulated NETs formation in pulmonary diseases including lung infections. Caudrillier *et al.* (2012) demonstrated that the platelets induced formation of NETs in transfusion related lung injury. Authors observed increased NETs levels in the patients with transfusion associated ARDS when compared to those who did not have ARDS [23]. Recent proteomics analysis revealed granule the content and the NETs forming ability of neutrophils which correlated with the incidence and severity of respiratory distress in pneumonia patients [24]. NETs components were elevated in broncho-alveolar lavage and correlated with IL-8 levels in subjects with pneumonia related ARDS [25]. In a randomized controlled trial in the community acquired pneumonia model, Ebrahimi *et al.* (2018) demonstrated increased serum NETs with clinical outcome [26]. In 100 human subjects with ventilator associated pneumonia with or without ARDS, Mikacenic *et al.* (2018) showed elevated levels of myeloperoxidase-DNA complex in alveolar space, suggesting NETs associated with local inflammation and bacterial burden in the lung [27]. Extracellular histones, component of NETs, were elevated in both the broncho-alveolar lavage fluid and plasma of ARDS subjects [28]. In rodent model of H1N1 influenza infection, increased neutrophils and NETs were noted in the lung which contributed to ARDS [29]. SARS-CoV-2 infected subjects showed significant mucous secretions similar to that of cystic fibrosis. Earlier studies have demonstrated that secretions in cystic fibrosis contains large

amount of NETs leading to impaired gas exchange and subsequent secondary infections [30]. Mounting evidences indicate substantial neutrophil recruitment in infected tissues of COVID-19 subjects (1, 6, 28). Interestingly, increased components of NETs such as cell free DNA, citrullinated histones and myeloperoxidase-DNA complexes in SARS-CoV-2 infected subjects were observed. Further, authors showed serum from COVID-19 patients induced NETs formation in the neutrophils of healthy subjects [22].

Interplay between oxidative stress and cytokines in NETs formation: implications in SARS-CoV-2 infections

Several studies have demonstrated that the SARS-CoV-2 infection is associated with dysregulated immune activation leading to cytokine storm. SARS-CoV-2 infection led to a significantly elevated systemic levels of cytokines such as IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, IL-17, IFNγ, IFNγ-inducible protein 10, monocyte chemo attractant protein 1 (MCP-1), G-CSF, macrophage inflammatory protein 1α (MIP-1α), and TNF-α which was associated with the respiratory failure, septic shock, coagulopathy and increased ferritin [31,32]. On the other hand, these inflammatory mediators have been shown to play a role in either life cycle of neutrophils or its function including NETs formation [34].

Analysis of 150 COVID-19 infected subjects from Wuhan, China, revealed significant elevation of C-reactive protein and IL-6 along with cardiac troponin and myoglobin, indicating a cytokine storm and fulminant myocarditis [35]. Interestingly, IL-6R blocking antibody Tociluzumab was beneficial in reducing immune dysregulation by increasing the lymphocyte count and HLA-DR expression in response to SARS-CoV-2 [36]. Neutrophils are known to shed sIL-6Rα in response to IL-6 [37] and studies have demonstrated the abundance of IL-6 in the SARS-CoV-2–associated cytokine storm [38,39]. Our earlier studies have shown IL-6 as one of the potential inducer of NETs and during Type 2 Diabetes, glucose modulated IL-6 induced NETs formation [40]. In a model of inflammation, we have also shown that human endothelial cells produce IL-8 during neutrophil-endothelial interactions which is responsible for inducing NETs and these NETs facilitated apoptosis in endothelial cells [41]. Elevated IL-1β in SARS-CoV-2 infected subjects is also known to induce NETs in aortic aneurysms and atherosclerosis [42–45]. TNF- α has been demonstrated to induce NETs *via* inducing oxygen free radicals and on the other hand, TNF- α is elevated in serum of SARS-CoV-2 subjects [39,31].

NETs formation is a redox sensitive process and requires either oxygen or nitrogen free radicals. Studies have shown involvement of both cytosolic and mitochondrial free radicals in the formation of NETs. Mutation(s) in any gene encoding for subunit of NADPH oxidase manifests in chronic granulomatous disease and infants suffering from this disease do not form intact NETs leading to lung infections [46]. This indicates NADPH derived oxygen free radicals is prerequisite to NETs formation. However, NOX independent NETs have also been demonstrated where mitochondrial ROS was prerequisite to form NETs [47]. Oxidant enzymes such as myeloperoxidase (MPO) is one of the key enzymes in the formation of NETs and MPO knockout mouse models failed to form intact NETs [48]. Reactive nitrogen species has also been shown to induce NETs. Accordingly, *in vitro* studies have shown antioxidants such as vitamin C, N-acetyl cysteine and enzyme inhibitors significantly abrogate NETs formation [49].

Immunomodulatory effects of Ayurvedic herbs

Over the centuries, Ayurveda the Indian system of medicine, has been in use to treat several infectious and non-infectious diseases. Ayurvedic herbs may significantly contribute towards prophylaxis and clinical management of SARS-CoV-2 infection due to their substantial immunomodulatory properties and re-establishment of immune homeostasis [50]. In the context of COVID-19 pathology, persistent infection leads to intense release of pro-inflammatory mediators (cytokine storm) which further results in enhanced inflammation subsequently leading to organ damage. Hence, the herbs possessing antiviral property along with the efficiency to maintain immune homeostasis with favourable Th1/Th2 cytokine balance might prove beneficial. Employing biochemical and cellular assays in *in vitro* in animals and clinical models, several studies have demonstrated immunomodulatory properties of various Ayurvedic herbs including *Tinospora cordifolia* (Guduchi), *Withania somnifera* (Ashwagandha), *Asparagus racemosus* (Shatavari), *Ocimum sanctum* (Tulsi), *Zingiber officinale* (Shunthi), *Cinnamomum zeylanicum* (Twak), *Emblica officinalis* (Amalaki), *Andrographis paniculata* (Kalmegh), *Phyllanthus niruri* (Bhumyamalaki), *Piper nigrum* (Maricha), *Piper longum* (Pippali), *Curcuma longa* (Haridra), *Glycyrrhiza glabra* (Yashtimadhu), *Adhatoda vasica* (Vasa), *Datura metal* (Kanaka), *Allium sativum* (Lashuna) and *Alstonia scholaris* (Saptaparna) in treating infectious and non-infectious diseases.

Ayurveda recognises communicable disease and epidemics [254]. Based on the clinical presentation, SARS-CoV-2 infection can be understood as a complex variant of Jvara (febrile conditions) involving all the Tridosha, with a dominance of Vata and Kapha. It mainly affects

the Pranavaha srotas (respiratory system) but can cascade to affect other systems in due course [51]. Hence, the various herbs explained by Charaka under Kasahara, Shwasahara, Jwarahara and Shirovirechana dashemani may help manage this condition. Most of the herbs discussed in the manuscript are Vata-Kaphahara, Krimighna (anti-microbial), Deepana (appetizer), Pachana (digesting), Rasayana (rejuvenation), Shothahara (anti-inflammatory) indicated in Kasa, Shwasa (respiratory ailments) and various types of Jvara (pyrexia). In the context of COVID-19 pathogenesis and associated neutrophil (dys)function, pharmacological activities of several Ayurvedic herbs can be potentially explored as a) anti-microbial to activate neutrophil function to eliminate infection, b) immuno-modulatory to minimize cytokine storm and thereby maintaining innate immune homeostasis and c) to inhibit over functioning neutrophils to form excess NETs which subsequently induce thrombosis. Experimental evidences demonstrating Ayurvedic herbs possessing aforementioned properties such as anti-microbial, immunomodulatory and anti-thrombotic effects along with the references are shown in Table 1.

Ayurvedic herbs possess anti-microbial properties

Based on Ayurveda scriptures, extensive studies have been carried out to demonstrate anti-microbial properties of Ayurvedic herbs and precisely have shown potential anti-viral effects in *in vitro, in vivo* and clinical settings [52–56]. Among them is *Terminalia chebula* which is widely used for the treatment of upper respiratory infections including cold and cough, and extensive research has shown that the fruit has anti-viral property against influenza A virus [57]. Studies have also demonstrated that treatment with the combination of Acyclovir (ACV) an anti-herpetic agent and *T. chebula* was effective for treating HSV-1 infection in mouse models [58]. Bioactive molecules such as chebulinic acid and chebulagic acid showed antiviral properties against HSV-2 and HIV [59].

Aqueous extract of *Phyllanthus niruri* exhibits strong mitogenic activity against murine lymphocytes and enhances the antigen presentation capability of dendritic cells. Mahalakshmi et al. (2015) experimentally demonstrated that different doses of aqueous *P. niruri* triggered the activation of neutrophils and consequently eliminated infections [60]. Studies have shown that *P. urinaria* extract inhibited formation and secretion of HBsAg and HBcAg by HBV in *in vitro* transient transfection model. Further studies showed that acetone, ethanolic and methanolic extracts of *P. urinaria* inhibited the HSV-2 viral infection [61]. Authors also demonstrated polyphenolic extract and gallic acid from *P. urinaria* exhibited anti-HIV-1 activities [61]. Procyanidin, a Phytochemical from *V. vinifera*, showed anti-

influenza A activity and could constrain the replication of virus at some stages of life cycle [55].

Active components of Glycyrrhiza such as glabridin, gabrin, glabrol, glabrene, hispaglabridin A, hispaglabridin B, 40-methylglabridin, and 3-hydroxyglabrol exhibited *in vitro* antimicrobial activity [62]. Studies have also demonstrated that antiviral activity of bioactive components such as ribavirin, 6-azauridine, pyraziofurin, mycophenolic acid and glycyrrhizin against SARS virus and glycyrrhizin has also been used for management of HIV-1 and chronic hepatitis C virus [62]. Aqueous and methanolic extracts of *Justicia adhatoda* has been demonstrated to possess antiviral activity against influenza virus upon inhibiting Hemagglutination (HA) [63].

Allium sativum exhibits broad range of anti-microbial activities. Allice, a chemical compound of garlic showed potential antimicrobial effect because of its chemical reaction with thiol groups of various microbial enzymes. *In vivo* study showed that garlic fights against intranasal inoculation with influenza viruses in mice models and further protected from virus responsible for common cold. Human *cytomegalovirus* (HCMV), influenza B virus, *herpes simplex virus* type 1, *herpes simplex virus* type 2, *parainfluenza virus* type 3, *vaccinia virus*, vesicular stomatitis virus and *human rhinovirus* type 2 are sensitive to garlic extracts [64]. Interestingly, independent studies have shown that above mentioned herbs such as ***T.*** *chebula* [52]*, P. niruri* [65] *, V.vinifera*[55]*, G.glabra* [66]*, J.adhatoda* [63] and *A.sativum* [67] significantly modulated neutrophil functions in disease conditions.

Ayurvedic herbs possess anti-inflammatory and anti-oxidant properties

Over the decades, innumerable studies have reported the anti-oxidant and anti-inflammatory properties of extracts prepared from hundreds of medicinally important plants. In the present manuscript, we have reviewed the Ayurvedic herbs, which significantly modulate neutrophil functions, and also exhibit anti-inflammatory and antioxidant properties. As pro-inflammatory cytokines induce NETs formation *via* redox sensitive pathways, we hypothesise that following herbs can be explored to inhibit over-functioning of neutrophils and NETosis, and help in clinical management of SARS-CoV-2 infections.

Both poly-herbal formulations and extracts of *T. cordifolia*, *W. somnifera* and *O. sanctum* reduced pro-inflammatory mediators including IL-1β, IL-6, IL-23, TNF-α and MIP-1 in mouse models of diseases associated with inflammation [68–70]. A study by Hasan *et al.*

(2016), demonstrated that administration of 200 mg/kg of *A. racemosus* root powder led to the reduction in the inflammatory cytokines level and neutrophil myeloperoxidase activity. Oral administration of methanolic extract of *A. racemosus* wild roots containing steroidal saponins reduced TNF-α, responsible for the expression of MCP-1 and VCAM-1 (vascular cell adhesion molecule-1), which are the key players leading to hyper inflammation state [71]. Treatment with aqueous *Z. officinale* extract in allergic airway inflammation reduced IL-13, IL-5 and IL-4 in OVA- immunized NOD/C57BL6/c mice [72,73]. Ethanolic extract of *C. zeylanicum* was tested on polymorphonuclear cells (PMNCs) stimulated with LPS, which showed reduced pro-inflammatory mediators such as IL-6 and TNF-α [74]. Piper species have been studied extensively for anti-bacterial, anti-mutagenic, anti-tumor, anti-diabetic, antioxidant and anti-inflammatory properties [75,76]. In allergic asthma model, *P. nigrum* extract reduced accumulation of inflammatory cells such as neutrophils and eosinophils in broncho-alveolar fluid (BALF) and mast cells in the pulmonary tissue. Further, authors showed cytokine production of Th1, Th2, Th17 and Treg cells were regulated and expression of IL-1β, IL-4, IL-6, IL-17A, RORγt, TNF-α and GATA3 were reduced upon treating with *P. nigrum* [77]. Herbs used in Ayurveda system such as Abhaya *(Terminalia chebula)*, Draksha *(Vitis vinifera)*, Kantakari *(Solamun xanthocarpum)*, Karkatashringi *(Pistacia integerrima)* Pushkara *(Inula racemosa)*, Shati *(Hedychium spicatum)*, Talisapatra *(Abies webbiana)* and Karkatashringi (*Pistacia integerrima)* has also been shown to possess antioxidant and immunomodulatory properties and significantly modulate neutrophil activity as indicated in Table no 1 and Figure 1.

Bioactive molecules of Ayurvedic herbs significantly modulate neutrophil functions including NETs formation

Traditional herbal preparations may consist of mixture of macro- and micromolecules which may directly or indirectly activate/inactivate or modify several targets with the fine balance of their PK/PD characteristics. A large array of alkaloids, polyphenols, flavonoids, terpenes, glycosides, saponins and many more may be present depending on the methods of herbal preparation. The constituent bioactive molecules of aforesaid herbs modulating a) neutrophil function, b) immunomodulatory and c) antioxidant properties have been detailed in Table 2. These bioactive molecules are subjected to ADME independently or through drug metabolizing enzymes (DMEs). DMEs are broadly categorized into three phases (phase I, II and III) that consists of enzymes and proteins to facilitate mechanisms and functions associated with ADME.

Steroidal alkaloids, sitoindosides VII–X, withaferin A and steroidal lactones extracted from *W. somnifera* shows significant anti-oxidant and free radical scavenging activities. Antioxidant enzymes such as catalase, SOD and GP_X increased upon the treatment of *W. somnifera* in rat brain [78]. In inflammatory mouse models induced by monosodium urate, Withaferin-A reduced the levels of TNF-α and enzymes such as β-glucronidase and lactate dehydrogenase in neutrophils [79]. Withanolide showed anti-inflammatory activity by suppressing superoxide anion generation and release of elastase in neutrophils stimulated by fMLP [80]. Integrated serum metabolomics and network pharmacology approach has demonstrated that Withanolides from *D. metal* leaves inhibit the production of inflammatory cytokines such as IL-1β, IL-6, IL-8, IFN-γ, TNF-α, HIF-1α and VEGF [81]. Ethanolic extract of *O. sanctum* contains Luteolin, Orientin, Urosolic acid, Apigenin7-Oglucuronide, Luteolin-7-O-glucuronide, Isorientin, Aesculin, Vallinin acid and Gallic acid and, these bioactive molecules significantly modulate inflammation including neutrophil functions [82]. A study by Nicolas *et al.* (2008) using bronchial epithelial cells, showed that *E. officinalis* extract containing pyrogallol possess anti-inflammatory effects and reduced the expression of the neutrophil chemokines such as GRO-α, GRO-γ, IL-8, ICAM-1 and of the pro-inflammatory cytokine IL-6 in IB3-1 cells [83]. *E. officinalis* is rich source of vitamin C and flavonoids. On the other hand, *in vitro* studies in human neutrophils showed flavonoids (−)-epicatechin, (+)-catechin hydrate, rutin trihydrate and vitamin C significantly inhibited PMA activated ROS production and extracellular DNA as measured by SYTOX green dye suggesting reduced NETs formation [49]. Quercetin, a major flavonoid present in several Ayurvedic herbs ameliorated inflammation in mouse model of Rheumatoid arthritis, where it inhibited neutrophil infiltration and NETs formation upon impeding autophagy. Authors demonstrated quercetin reduced the expression of citrullination of histones and PAD4 in ankle joints indicating decreased NETs formation in arthritis models [84]. Influence of quercetin hydrate on reducing NETs formation was also demonstrated in bovine neutrophils [85]. Andrographolide is one of the bioactive molecules found in *Andrographis paniculata*. Maria *et al.* (2013) reviewed several studies and proposed underlying mechanisms for the anti-inflammatory and pro-inflammatory properties of andrographolide. Andrographolide decreased COX-2 expression in neutrophils and further modulated NF-κB pathway, inhibited effect of iNOS and COX-2 expression in macrophages and activated transcription factors AP-1 and STAT3 to produce pro-inflammatory cytokines such as IL-1β, IL-6 and IL-10. In the T-cells of rheumatoid arthritis mouse models, andrographolide induced Nuclear Factor of

Activated T cells (NFAT) levels [86]. Li et al. (2019) have demonstrated reduced neutrophil infiltration and NETosis in ankle joints in adjuvants induced arthritis murine models by andrographolide and further showed inhibition of LPS induced autophagy dependent NETs [87]. Immunostaining of murine rheumatoid arthritis ankle showed increased PAD4 and citrullinated histone levels and further, andrographolide treatment significantly reduced these components of NETs [69]. In the context of influence of flavoured e-cigarettes, cinnamaldehyde, a major bioactive constituent of C. *zeylanicum,* inhibited PMA activated NETs formation and also phagocytic ability of neutrophils [88]. Authors demonstrated that cinnamaldehyde decreased extracellular DNA by fluorimetry and immunofluorescence [70]. In clinical models of lupus and antiphospholipid syndrome (APS), gingerol, an important constituent of ginger root, reduced the DNA associated myeloperoxidase activity indicating abrogating NETs formation induced by ribonucleoprotein (RNP)/anti-RNP complexes and antiphospholipid antibodies (aPL) from APS patients [89]. Kanashiro et al. (2007) examined the ability of flavonoids such as myricetin, quercetin, kaempferol and galangin on neutrophil degranulation and demonstrated quercetin as potent inhibitor of neutrophil elastase release induced by fMLP [90]. Kaempferol is one of the major bioactive molecules of Ayurvedic herbs and recent study showed that kaempferol inhibited lung metastasis in mouse breast cancer models by blocking NADPH/PAD4 dependent NETs formation [91].

The antioxidant traits possessed by *P. niruri* may be due to the chemical constituents such as lignans, flavonoids, tannins and terpenes. *P. niruri* in the polyherbal form showed nitric oxide scavenging properties [92]. A new class of amide alkaloid compounds from *P. nigrum* – Pipernigramides A-G (42-44) reduced inducible nitric oxide synthase (iNOS)-mediated NO and IL-1β, IL-6, TNF-α, and PGE2 release in RAW 264.7 cells activated with lipopolysaccharide [93]. Curcumin, active metabolite of *C. longa* has been extensively studied for its anti-inflammatory activity. Both *in vitro* and *in vivo* studies showed curcumin attenuated random migration and polarization of neutrophils against conditioned medium of LPS activated macrophages. Further, authors demonstrated curcumin effects were due to inhibition of PI3K/Akt led actin polymerization at leading edge of neutrophils [94]. Curcumin treatment for Benzo-a-pyrene (BaP) exposure effectively reduced inflammatory cytokines IL-6, TNF-α and C-reactive protein (CRP) levels in mice model indicating a possible role in BaP lung injury [95]. Curcumin regulated immune response upon reducing synthesis of local inflammatory mediators *in vitro* and in mice infected with Influenza A

virus [96]. Curcumin pre-treated mice when exposed to reovirus 1/L-mediated acute viral pneumonia showed modulation of expression of IL-6, IL-10, IFNγ, and MCP-1 through a reduction in the phosphorylated form of NFκB p65. TGF-ß Receptor II was significantly reduced and expression of α-smooth muscle actin and Tenascin-C was inhibited. Silver nanoparticles infused with Curcumin decreased titres of respiratory syncytial virus by directly inactivating the virus thereby preventing the host cells from infection [97,98].

Ayurvedic herbs regulate upstream signalling events of NETs formation: implications to COVID -19 management

Toll like receptor (TLR) signalling, autophagy and hypoxic conditions are known signalling effectors/mediators which are associated with NETs formation in response to various pathophysiological stimuli and on the other hand, COVID-19 pathology is also associated with significant modulation of above signalling components. Hence, Ayurvedic herbs may modulate these mediators by potentially reducing the NETs formation. TLR4 activation by PAMPs facilitates the neutrophil recruitment at the site of infection either directly (by the activation of TLR by the endothelial cells) or indirectly (by the cytokines). TLRs expressed on the neutrophils have been demonstrated to activate NF-κB pathway and release of pro-inflammatory cytokines [99]. Li et al. (2017) suggested that pathogenesis of ventilator induced lung injury was associated with NETs formation and the lower level of NETs components were detected in the TLR4-KO mice supporting the hypothesis of TLR4 dependent NETs formation during lung injury [100]. A molecular docking study by Choudhary et al. (2020) demonstrated the interaction of SARS-COV-2 spike protein and human TLR4 providing a promising strategy to target the TLR4 activation induced by SARS-COV-2, as the inflammatory mediators such as IL-6 and TNF-α involved in the "cytokine storm" are the downstream regulator of TLR4 signalling pathway [101]. Interestingly, studies have shown that Auyrvedic herbs modulate TLR4 signalling. Schink et al. (2018) demonstrated that phytochemicals such as trans-cinnamaldehyde and p-cymene in the cinnamon bark extract reduced LPS-dependent IL-8 secretion in THP-1 monocytes upon modulating the TLR4 pathway [102]. Another study demonstrated decreased IL-6 production by quercetin in the human PBMCs induced with oxidized-LDL suggesting the downregulation of TLR-NF-kB signalling axis [103]. NETs formation is also associated with release of metalloproteinase [104]. Using *in silico* approaches, Kanbarker and Mishra (2020) showed that the polyphenol compounds such as epigallocatechin-3-gallate and theaflavin

possess the ability to inhibit the MMPs against SARS-COV-2 main protease suggesting the beneficial role in COVID-19 prophylaxis [105]. Heinemann et al. (2016) showed the NETs formation in response to viable *S. aureaus* in hypoxic conditions [106]. The new insight of "happy hypoxia" in the COVID-19 cases shows the importance of targeting hypoxia inducible factor -1 (HIF-1) activation, which contributes to the pathophysiology of ischemic cardiovascular disorders and pulmonary diseases. Interestingly, Ouyang et al. (2019) showed the inhibition of HIF-1α induced inflammation and apoptosis in macrophage by curcumin, the phytochemical obtained from turmeric, *via* ERK dependent pathway [107].

Kinetics of activation of antioxidant and pro-inflammatory pathways is unclear

The relationship between anti-oxidants and cytokine release is a double edged sword. While oxidants can activate cytokines; under different circumstances, cytokines can also activate oxidants and all of these are driven by several transcriptional and post-transcriptional events. Both oxidants and cytokines can induce NETosis. Besides, mitochondria also play a central role to maintain the fine balance between reactive oxygen species and cytokine production. It is critical to maintain the neutrophil function such as degranulation, phagocytosis and chemotaxis without excessive NETs formation. In the local microenvironment upon infection and if not adequately oxygenated, infiltration of neutrophils can cause hypoxic conditions due to excess oxygen consumption to release reactive oxygen species [108]. Hypoxic conditions, such as in ARDS, may inhibit radical formation, extend the life span of neutrophils, yet retain its function to induce degranulation and release pro-inflammatory cytokines [109]. However, these subjects are not within the purview of this review as already a number of articles are published on these topics. Nevertheless, these and more intricate multifactorial imbalances leading to altered phenotypes cannot be restored with a single drug for a normal homeostasis. Therefore, multiple constituents of a single herb or multiple herbs may be required to influence the pathways either sequentially or parallelly to cause induced additive, antagonistic and/or synergistic effects.

Ayurvedic herbs regulate downstream effects of uncontrolled NETosis and concomitant thrombosis: implications to COVID-19 pathogenesis

Studies suggests potent pro-inflammatory, pro-thrombotic and cytotoxic properties of NETs and their implications in th epathogenesis of thrombosis and associated diseases [110]. On the other hand, recent data indicate COVID-19 pathogenesis is significantly associated with thrombotic microangiopathy *via* platelet/NETs/thrombin axis [111,112]. Multifaceted role of

neutrophils in the pathogenesis of stroke has been demonstrated and targeting neutrophils showed ameliorated stroke progression [113]. Involvement of NETs have been demonstrated both in arterial and venous thrombosis. Fuchs et al. (2010) demonstrated NETs in the blood upon perfusion resulted in platelet activation, aggregation and recruitment of RBC and fibrin for clotting. This was abrogated by the addition of DNase, suggesting NETs can potentially cause thrombosis and NETs were enriched in thrombus in Baboon DVT model [114]. In a transient middle cerebral artery occlusion model for stroke, administration of DNase I and neutralizing antibodies against histone led to smaller infracts [115]. Mechanistically, both neutrophils and platelets are known to activate each other either via P-selectin and β2/ β3-integrins or cytokine/complement (IL-1β, TNF-α, GM-CSF, C3a, C5a) may mediate TREM-1 receptor interaction, which leads to IL-8 release resulting in recruitment neutrophils causing tissue injury [116].Using human iliac artery biopsies, Wohner et al. (2012) demonstrated neutrophil derived elastase and metalloproteases degraded vWF promoting platelet adhesion. In severe inflammatory conditions of sepsis, activated platelets induced TLR mediated NETs [117].

Earlier studies have explored several Ayurvedic herbs in the management of thrombosis and associated diseases. Using rat model, Shen et al. (2004) showed extracts of *Phyllantus urinaria* containing corilagin prolonged occlusion time of carotid artery, reduced thrombus and decreased platelet-neutrophil interaction [118]. *Vitis vinifera* seed extract containing proanthocyanidins reduced pro-inflammatory mediators such as IL-6, IL-8, TNF-α and further decreased platelet aggregation and thrombus formation in rat deep vein thrombosis models [119]. Methanolic extracts of *Solanum xanthocarpum* and *Tinospora cordifolia* showed anti-thrombotic activity by significantly inhibiting thrombin induced platelet aggregation [120]. Lee et al. (2017) showed Zingerone (ZGR) is an anti-FXa and anti-platelet compound that inhibited intrinsic blood coagulation pathways through FXa. ZGR a bioactive component of ginger inhibited human platelet aggregation in response to various agonists in *in vitro* model induced by ADP and U46619 (a stable thromboxane A2 analog/aggregation agonist) in a dose-dependent manner. In an another study, ZGR also exhibited anti-thrombotic property in mouse models, treated with ferric chloride ($FeCl_3$) to induce carotid artery thrombosis in mice [121]. Glycyrrhizin (GL) is compound extracted from *G. glabra*, showed anti-thrombotic effect in *in vivo.* In two different experimental models of induced thrombosis in rats, intravenous administration of GL showed dose-dependent reduction in

thrombus size and hypercoagulability [122]. Interestingly, independent studies have shown Phyllantus [65], Vitis [123], Ginger [89] and glycyrrhiza [66] significantly modulates neutrophil function. Taken together, these Ayurvedic herbs might help both to inhibit NETs production and its consequences on platelet aggregation in COVID-19 pathogenesis.

Conclusion

Clearly, excessive NETosis of neutrophils, the abundant white blood cells in circulation of innate immune system, is activated by autocrine and paracrine factors, metabolites and free radicals in an uncontrolled fashion. Our understanding of the activation of neutrophils, especially in conditions such as SARS-CoV-2 infection, is incomplete. Similarly, there is also a significant gap in our understanding of a) how oxidants and cytokines regulate each other under normal and disease states, b) their key molecular determinants, c) components of the ayurvedic herbal preparations that may target events of specific pathways and restore neutrophil function and d) impact of traditional therapy on other related innate and acquired immune functions. The challenge to overcome is the need to dive deeper to unravel new concepts and mechanisms towards translation relevant to traditional medicine practices.

In the context of neutrophil (dys)function in COVID-19 pathogenesis, Ayurvedic herbs might potentially act a) as anti-microbial by activating neutrophils to eliminate infection, b) to reduce over-functioning of neutrophils and NETs formation by inhibiting cytokine production thus maintaining immune homeostasis and c) to control NETs induced platelet aggregation, thereby reducing thrombosis and coagulation. In search of Ayurvedic herbs, we found Amalakki, Ashwagandha, Bhumyamalakki, Dattura, Draksha, Guduchi, Haridra, Kalmegha, Kantakari, Lashuna, Shunthi and Tulasi exhibiting all these properties and hence, we suggest Auyrvedic preparations from these might be beneficial for the management of the COVID-19. However, Ayurveda also describes a personalized medicine strategy based on Prkirti and Tridoshas and hence, integration of may be necessary towards effective strategies to combat the disease.

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Figure Legends

Figure 1. Influence of Ayurvedic herbs in modulating neutrophil functions and its potential role in COVID-19 management.

Examples of representative Ayurvedic herbs containing bioactive molecules might act as a) anti-viral, b) inhibit formation of NETs by reducing cytokine storm due to the excess release of pro-inflammatory mediators such as IL-6, IL-10, TNF-α, c) reduce NETs formation to decrease platelet aggregation and thrombosis.

Table Legends

Table 1: Charaka Samhita and Bhavaprakasha references for Ayurvedic herbs with therapeutic properties to target respiratory system along with evidences to modulate neutrophil functions.

Table 2: Pharmacologically active compounds in Ayurvedic herbs and their role in modulating inflammation.

Table 1: Charaka Samhita and Bhavaprakasha references for Ayurvedic herbs with therapeutic properties to target respiratory system along with evidences to modulate neutrophil functions [255, 256]

Ayurvedic herb (Botanical name)	**Properties & indication as per Ayurveda**	**Dose/ Model**	**Function in relation to neutrophil activity in COVID-19**	**Reference**
Abhaya *(Terminalia chebula)*	Jwaraghna, Tridoshahara, (mitigates 3 Doshas) Deepana (appetizer), Rasayani (rejuvenation), Bruhmana (nourishing), Shwasa-Kasahara (respiratory disorders), Shotha hara (anti-inflammation), Krimihara (anti-microbial), Vishama Jwara (intermittent fever)		a) Antimicrobial b) Immunomodulatory	[52,59,124–126]
		In vivo: 50-62.5 mg/kg/d for 5 weeks Bovine type II Collagen induced arthritis DBA/1J mice	Suppresses the production of TNF-α, IL-6 and IL-1β in a dose-dependent manner	
		In vitro: 20-80µg/ml LPS-induced mice microglial cell	Decreases TNF-α, IL-1β, IL-6, PGE-2, COX-2	
		In vivo: 100mg/kg, p.o. for 4 days in male Wistar rats	Increases IL-2, IL-10 and TNF-α	

		In vivo: 1g/kg/d p.o. for 48days with saline in male albino rats	Triphala contains *T. chebula* as a main ingredient Enhances neutrophil function	
Amalaki (*Emblica officinalis*)	Jwaragna, Tridoshahara, (mitigates 3 Doshas) Deepana (appetizer), Rasayani (rejuvenation), Bruhmana (nourishing), Shwasa-Kasahara (respiratory disorders), Shothahara (anti-inflammation), Krimihara (anti-microbial), Vishama Jwara (intermittent fever)		a) Antimicrobial b) Immunomodulatory c) Antithrombotic	[52,83, 127–131]
		In vitro: 500µg/ml IB3-1cells from cystic fibrosis patient	Inhibits the PAO1-dependent expression of the neutrophil chemokines IL-8, GRO-α, GRO-γ, of the adhesion molecule ICAM-1 and of the pro-inflammatory cytokine IL-6.	
		In vivo: 200mg/kg from day 15 in male albino Wistar rats	Reduces IL-1β, IL-18 and capase-1	
		In vivo: 540mg/kg p.o. for 7 days in albino rats of either sex by Carrageenan induced rat paw edema method	Decreases neutrophil count	
		In vivo: 5mg/kg p.o. for 3 days, in male Swiss Albino mice	Gallic acid reduces neutrophil infiltration	
		In vitro: 1g/kg/d for 48days, in male albino rats with indomethacin induced gastric ulceration	Triphala contains *E. offoconalis* as a main ingredient Increases the neutrophil adhesion in noise stress induced mice	
		In vitro: 20-500µg/ ml Dendritic cells (DC) derived from murine bone marrow of C57BL/6 mice	Chyawanaprasha contains 90% *E. officinalis* Increases cytokines IL-1β, TNF-α and MIP-1α	
Ashwagandha (*Withania somnifera*)	Balya (provides strength), Bruhmana, Shothahara (anti-inflammatory), Kapha-vatahara (mitigates kapha-vata), Rasayana (rejuvenation)		a) Antimicrobial b) Immunomodulatory c) Antithrombotic	[69,132–137]
		In vitro: <5mg/ml Human keratinocyte cell line HaCaT	Inhibits mRNA expression of inflammatory cytokines such as IL-8, IL-6, TNF-α, IL-1β, IL-12	

			Elevates anti-inflammatory cytokine TGF-β1 Inhibits NF-κB pathway	
		In vivo: 20µl; 10mg/ml by topical application for 5 days, C57BL/6J mice with wounded skin	Inhibits mRNA expression of TNF-α Increases anti-inflammatory cytokine TGF-β1	
		In vivo: 400mg/kg p.o. once a week for 4 weeks, male Swiss albino mice with Azoxymethane-induced colon cancer	Increases neutrophil count	
		In vivo: 10mg/kg/d day 5 to 21 by gastric intubation in adult male Wistar rats with induced arthritis by intradermal injection of 0.1 ml of 0.1% Freud's Complete Adjuvant (FCA)	Jeevaneeya Rasayana contains *W. somnifera* as a main constituent Down regulates pro-inflammatory cytokines TNF-α, IL-6 and MMP-9	
		In vitro: 0.00001053-10.53 µg/mL in LPS-induced spleenocytes of C57BL/66 male mouse	Herbo-mineral formulation contains *W. somnifera* Reduces TNF-α, IL-1β and MIP-1α Elevates IFN-γ levels	
Bhumyamalaki *(Phyllanthus niruri/Phyllanthus urinaria)*	Kasahara, Shwasahara, Kapha-pitta hara (mitigates kapha-pitta)		a) Antimicrobial b) Immunomodulatory c) Antithrombotic	[60,61, 118,138]
		In vivo: 2 µg-2 mg (w/v) i.p. *Oreochromis mossambicus* fish of either sex	Enhances neutrophil activation	
		In vitro: 1.56 to 25µM, LPS-activated U937 cells	Phyllanthin inhibits IL-1β, TNF-α, PGE_2 and COX-2 expression	
Dhatura/ Kanaka *(Datura metel)*	Jwarahara (mitigates fever), Kapha vata shamaka (mitigates kapha-vata), Krimihara		a) Antimicrobial b) Immunomodulatory c) Antithrombotic	[54,139–141]

	(anti-microbial)	*In vivo:* 1.23 and 2.46ml/kg p.o. for 28 days, in male Wistar rats sensitized with ovalbumin 40mg and aluminium hydroxide 2.0mg *In vivo:* 0 to 0.08ml/kg SC for 10 days in Western African Dwarf bucks	*D. metel* is the major ingredient of Kanakasava Inhibits IL-4, IL-5, IL-1β and TNF-α Reverses elevated neutrophil in blood & BALF Increases neutrophils counts	
Draksha *(Vitis vinifera)*	Jwara (pyrexia), Kasa-Shwasa (respiratory ailments), Swarya (voice enhancer), Raktapitta (bleeding disorders), Bruhmana (nourishing)	*In vivo:* 0.9-5.1ng/ml, in adult male Wister rats	a) Antimicrobial b) Immunomodulatory c) Antithrombotic Decreases neutrophil migration in response to LPS	[55,119,123]
Guduchi *(Tinospora cordifolia)*	Tridoshahara, Rasayani (rejuvenation), Balya (provides strength), Agni deepana (appetizer), Kasa (cough), Jwara (pyrexia), Krimi (anti-microbial).	*In vivo:* 300mg p.o. for 8 weeks, human clinical trial *In vivo:* 1g/kg in 2ml volume p.o. from day 9 to 19 in Male Lewis rats adjuvant induced arthritis model *In vivo:* 50 mg/kg p.o. for 7 days, in Charles Foster strain albino rats of either sex using carrageenan induced paw edema model	a) Antimicrobial b) Immunomodulatory c) Antithrombotic Decreases neutrophil & basophils in nasal smear Reduces pro-inflammatory mediators IL-1β, IL-6, IL-23, TNF-α and MIP-1 Guduchi Ghana contains *T. cordifolia* Anti-inflammatory activity	[56,68,120,142–144]
Haridra *(Curcuma longa)*	Krimighni (anti-microbial), Kapha-pitta hara (mitigates kapha-pitta) Shirovirechana	*Ex vivo:*50µM Mouse colonic epithelial cells (YAMC) Intra-peritoneal	a) Antimicrobial b) Immunomodulatory c) Antithrombotic Curcumin effectively reduced LPS-stimulated chemokine secretion MIP-2, IL-1β, MIP-1α	[53,94,97,145,146]

		macrophages from BALB/c mice		
		In vivo: 100µg/g in 80µl injection volume i.p. Male BALB/c mice post treatment peritonitis induction.	Inhibits random neutrophil migration	
		In vitro: 1µM-1mM, Polymorphonuclear cells from Rhesus monkey	Curcumin inhibits neutrophil aggregation	
		In vivo: 50mg/kg i.p. CBA/J mice Reovirus 1/L-induced acute viral pneumonia model	Curcumin modulates expression of IL-6, IL-10, IFNγ, and MCP-1 Reduces TGF-ß Receptor II	
Kalamegha *(Andrographis paniculata)*	Deepana (appetizer), Kapha-pitta hara (mitigates kapha-pitta), Krimighna (anti-microbial), Jwara (pyrexia)		a) Antimicrobial b) Immunomodulatory c) Antithrombotic	[147–149]
		In vitro: 0.1-1µM Human neutrophils	fMLP-induced adhesion and transmigration of peripheral human neutrophils was prevented	
Kantakari *(Solamun xanthocarpum)*	Shvayahtuhara (anti-inflammatory), Kapha-vatahara (mitigates kapha-vata), Deepana (appetizer), Pachana (digestive), Kasa-Shwasa (respiratory ailments), Jwara (pyrexia), Krimihara (anti-microbial), Pinasa (rhinitis)		a) Antimicrobial b) Immunomodulatory c) Antithrombotic	[120,150–153]
		In vivo: 50-200mg/kg/d p.o. for 22 days in Wistar rats of either sex induced with ovalbumin	Reduces TNF-α Suppresses IL-6 and IL-4 Elevates IFN-γ	
		In vivo: 100mg/kg p.o. for 14 days. Swiss albino mice	Increases neutrophil adhesion	
		In vivo: p.o. 11 days treatment in Albino rats	Decreases neutrophil percentage and cytokine induced neutrophil chemoattractant 1(CINC-1)	
Karkatashringi *(Pistacia*	Kapha-vatahara (mitigates kapha-vata), Jwara (pyrexia),		a) Antimicrobial b) Immunomodulatory	[154–156]

integerrima)	Shwasa-Kasa (respiratory ailments), Aruchi (tastelessness), Vami (vomiting)	*In vivo:* 7.5 to 30mg/kg i.p. Female Sprague-Dawley rats, Male Dunkin Hartley, Guinea pigs Swiss albino mice.	Inhibits LPS induced neutrophilia Reduces LPS induced neutrophil adhesion and cytokine release (TNF-α, IL-1β and IL-6)	
Lashuna *(Allium sativum)*	Bruhmana (nourishing), Kapha-vata hara (mitigates kapha-vata), Rasayana (rejuvenating), Jeerna jwara (chronic fever), Kasa hara (mitigates cough)	*In vitro:* Endothelial cell monolayers from human umbilical endothelial cells *In vivo:* 80mg/kg p.o. for 4 weeks. Dermatophagoides pteronyssinus (Der p) induced allergic asthma mice model	a) Antimicrobial b) Immunomodulatory c) Antithrombotic Inhibits neutrophil migration Increases Th1 cytokines IFN-γ and IL-12 Reduces Th2 cytokines IL-13, IL-4 and IL-5 Inhibits expression of IL-1β, IL-6 and TNF-α	[64,157–160]
Maricha *(Piper nigrum)*	Deepana, Krimighna, Shirovirechana, Kapha-vatahara (mitigates Kapha-vata), Deepana (appetizer), Shwasa (respiratory disease), Shoola (pain), Krimi (microbes)	*In vitro:* 50-100µg/mL in BALB/c mice spleenocytes. *In vivo:* 200mg/kg p.o. day 15 to 26 in female BALB/c mice Ovalbumin induced allergic asthma model	a) Antimicrobial b) Immunomodulatory Inhibits IL-4 and IL-10 Enhanced IFNγ Decreased neutrophil count Regulates cytokine production of Th1, Th2, Th17 and Treg cells Inhibits IL-1β, IL-4, IL-6, IL-17A, RORγt, TNF-α and GATA3 Increases IL-10, INF-γ	[77,161–163]
Pippali *(Piper longum)*	Deepana, Triptighna, Kantya, Shirovirechana, Vata-Kaphahara (mitigates vata- kapha), Deepana (appetizer), Rasayana (Rejuvenation), Krimi (Anti-microbial), Jwarahara (Antipyretic), Shoola (pain) Shwasa-Kasa (Respiratory	*In vitro:* 17.5µg/ml. Human endothelial cells *In vivo:* 10-100mg/kg p.o. in C57BL/6 mice with cerulein induced acute pancreatitis	a) Antimicrobial b) Immunomodulatory Inhibits TNF-α-induced adhesion of neutrophils to endothelium monolayer Piperine reduces production of TNF-α, IL-1β & IL-6 Reduces acute pancreatitis induced neutrophil infiltration	[164–166]

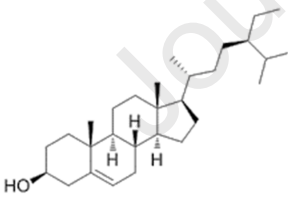
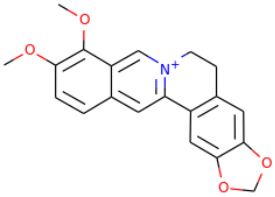
	ailments), Jeerna Jwara (Chronic fever)			
Pushkara *(Inula racemosa)*	Kapha-vatahara (mitigates kapha-vata), Jwara (fever), Shotha (anti-inflammatory) Kasa-shwasa (respiratory ailments), Aruchi (tastelessness)	*In vivo:* 500mg/kg p.o. for 14 days in Swiss albino mice of either sex	a) Antimicrobial b) Immunomodulatory Bharangyadi compound containing *I. racemosa* showed increase in neutrophil adhesion.	[167–171]
Saptaparna *(Alstonia scholaris)*	Shirovirechana, Shleshma-vata hara (mitigates kapha-vata hara), Shwasahara	*In vivo:* 50-200mg/kg in BALB/c mice *In vitro:* 1-25µg/ml. in human neutrophils *In vivo:* 10-50mg/kg p.o in male Sprague-Dawley rats induced with Ovalbumin	a) Antimicrobial b) Immunomodulatory Increases phagocytic index Increases respiratory burst in Polymorphonuclear neutrophils Inhibits inflammatory mediators TNF-α and IL-8 Reduces IL-4 level	[172–174]
Shatavari *(Asparagus racemosus)*	Balya (provides strength), Vata pitta hara (mitigates vata-pitta), Agni pustida (increases digestive power), Rasayani (rejuvenation), Shothajit (anti-inflammatory)	*In vivo:* 100mg/kg/d p.o. 15 days in Swiss albino mice with cyclophosphamide induced neutropenia *In vivo* 200mg/kg i.p. in male C57BL/6 mice	a) Antimicrobial b) Immunomodulatory Increases absolute neutrophil Inhibits TNF-α and IL-1β Reduces inflammatory cytokines level and neutrophil myeloperoxidase activity	[71,175,176]
Shati *(Hedychium spicatum)*	Shwasahara, Kapha-vatahara (mitigates Kapha-vata), Shothahara (anti-inflammatory), Shwasa-Kasa (respiratory ailments), Shoolahara (analgesic)	*In vivo:* 200-500mg/kg p.o. for 15 days in Swiss albino mice and albino rats. Ovalbumin induced allergic asthma	a) Antimicrobial b) Immunomodulatory Increases neutrophil count	[177,178]
Shunthi *(Zingiber officinale)*	Kapha-vatahara (mitigates Kaphavata), Ruchya (enhances taste), Pachana (digestion),		a) Antimicrobial b) Immunomodulatory c) Antithrombotic	[72,121,179,180]

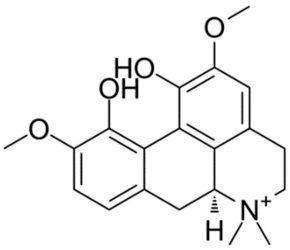
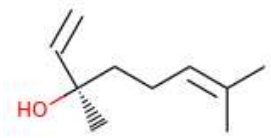
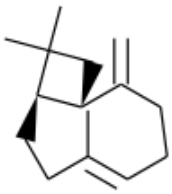
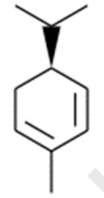
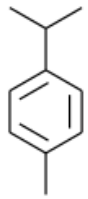
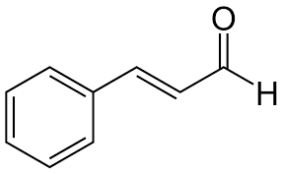
	Swarya (enhances voice), Shwasa-Kasa (respiratory ailments), Shoola (pain), Shopha (inflammation)	*In vivo:* 500mg/kg and 720mg/kg i.p. in Male BALB/c mice	Decreases neutrophils in BALF Lowers IL-4 and IL-5	
		In vivo: 45 to 720mg/kg i.p. day 7 and 8 in NOD mice and C57BL/6 mice Ovalbumin induced	Reduces IL-5 and IL-4	
Talisapatra *(Abies webbiana)*	Shwasa-Kasa (respiratory ailments), Kapha anila apaha (mitigates kaphavata), Aruchi (tastelessness), Vahnimandya (decreased appetite)		a) Antimicrobial	[181]
Tulasi (*Ocimum sanctum*)	Shwasahara Kapha-vatajit (mitigates kaphavata), Deepana (appetizer), Bhutagni (anti-microbial), Kasa-Shwasa (respiratory ailments)		a) Antimicrobial b) Immunomodulatory c) Antithrombotic	[70,182–186]
		In vivo: 100mg/kg i.p. for 45 days in Wistar strain male albino rats	Enhances phagocytic activity of neutrophil	
		In vivo: 250mg/kg p.o. for 20 days in Albino Wister rats	Enhances IL-2	
		In vitro: 25-500µg/ml in Spleenocytes		
		In vivo: 250mg/kg for 20 days in Wistar albino rats of either sex. Excision model of wound repair	Up regulates TNF-α production	
		In vivo: 850mg/kg p.o. for 15 days in Swiss albino mice	Elevates IL-2, IL-4, TNF-α and IFN- γ Reduces IL-1β and NF-kB levels	
Twak (*Cinnamomum zeylanicum*)	Anila pitta hrut (mitigates vata pitta), Aruchi (tastelessness), Pinasa (rhinitis), Kasa (respiratory ailments), Krimi (anti-microbial)		a) Antimicrobial b) Immunomodulatory	[187–189]
		In vivo: 10-100mg/kg p.o. for 10 days in Albino Wistar rats	Increases neutrophil adhesion	

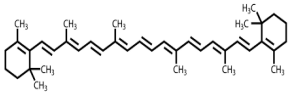
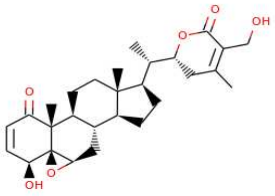
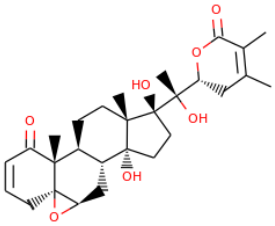
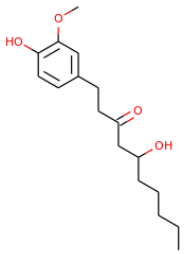
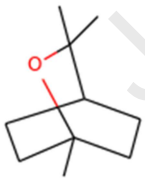
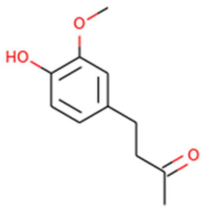
				Inhibits pro-inflammatory cytokines especially IL-1β, IL-6 and TNFα	
Vasa (*Adhatoda vasica*)	Kapha-pitta-raktahara (mitigates kapha-pitta-rakta), Shwasa-Kasa (respiratory ailments), Jwara (pyrexia)			a) Antimicrobial b) Immunomodulatory c) Antithrombotic	[63,190–193]
		In vivo: 10gm/kg	28 days in humans (Clinical study)	*A. vasica* given in Leha form showed decrease in neutrophils. Bromhexine a derivative of *A. vasica* has mucolytic activity	
		In vivo: 400mg/kg p.o. for 8 days in male Wistar rats		Increases adhesion of neutrophils to nylon fibers	
Yastimadhu *(Glycyrrhiza glabra)*	Pitta-anila-asra jith (mitigates pitta-vata-rakta), Shothahara (anti-inflammatory), Ruchya (enhances taste), Rasayana (rejuvenation)			a) Antimicrobial b) Immunomodulatory c) Antithrombotic Antitussive, expectorant, antimicrobial, antiviral, anti-oxidant, anti-inflammatory, immune-modulatory activity	[66,122,194–197]
		In vitro: 25-100µg/ml	in RAW 264.7 macrophages stimulated with LPS	Inhibits LPS-induced TNF-α, IL-1β, IL-6 production	
		In vitro: 50-200µg/ml	in LPS-stimulated mouse endometrial epithelial cells	Glycyrrhizin inhibits LPS-induced TNF-α, IL-1β, NO & PGE_2 production	
		In vitro: 200, 40, 8mg/l	in LPS-induced macrophage cell line of RAW264.7	Glycyrrhizin acid supresses IL-1β, IL-3, IL-5, IL-10, IL-12, IL-13 & TNF- α (LPS stimulated)	
		In vivo: 50 to 100mg/kg p.o. for 11 days in Male BALB/c mice.		*G. Glabra* with 2 more herbs inhibits airway inflammation by inhibiting inflammatory cytokines TNF- α, IL-17A, IL-6, COX-2	

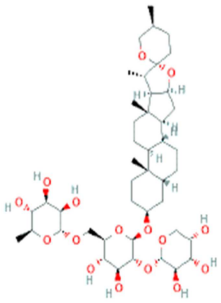
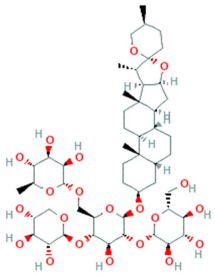
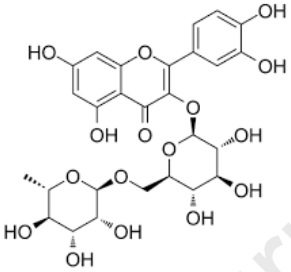
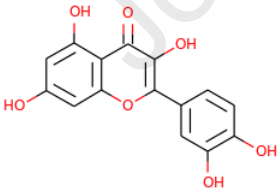
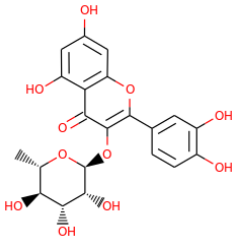
p.o: per oral; i.p: intra-peritoneal; SC-subcutaneous

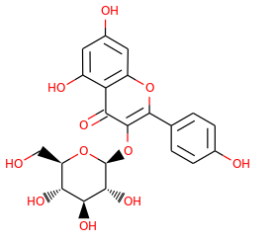
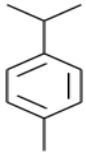
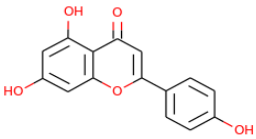
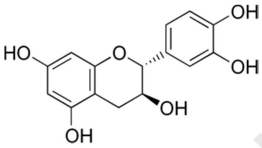
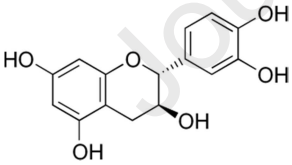
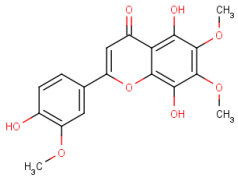
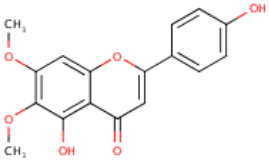
Table 2: Pharmacologically active compounds in Ayurvedic herbs and their role in modulating inflammation

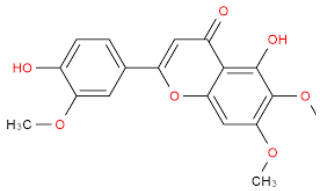
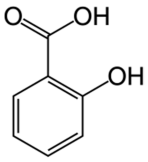
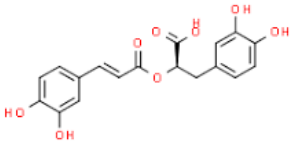
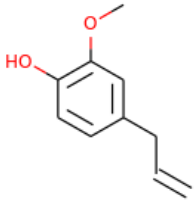
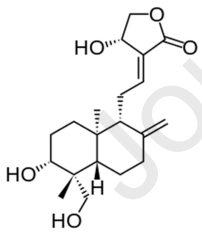
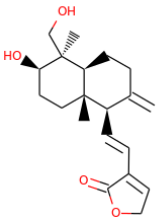
Name of the herb	Phytochemical name	Function	Reference
Tinospora cordifolia	β-sitosterol 	Anti-inflammatory	[198]
		Increases neutrophils count	[199]
		Inhibits secretion of TNF-α, IL-1β, IL-6, IL-8	
		Reduces NLRP3 and capase-1	
	Berberine 	Anti-inflammatory	[200]
		Downregulates MCP-1, IL-6, TNF-α	
		Attenuates the inflammation in the air way by inhibiting neutrophil infiltration	[201]
	Magnoflorine	Anti-inflammatory, immuno-modulatory, antioxidant activity	[202]

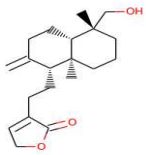
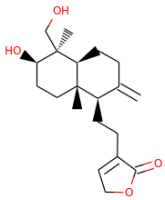
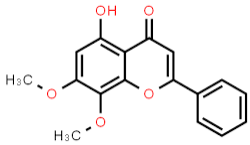
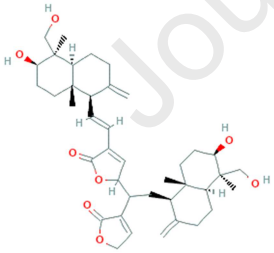
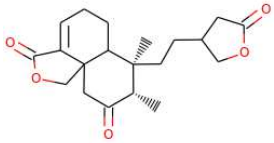
			
Cinnamomum zeylanicum	(-)-Linalool 	Inhibits eosinophil numbers, Th2 cytokines and IgE levels Prevents the influx of inflammatory cells and hyper secretion of mucus	[203]
	Beta-caryophyllene 	Inhibits of neutrophil migration in Cg-induced peritonitis mice model Decreases in TNF-α, IFN-γ, IL-4, IL-5, IL-6	[204]
	(+)-alpha-phellandrene 	Prevents induction of Neutrophil accumulation Inhibits TNF-α and IL-6	[205]
	p-cymene 	Reduces total leukocyte and neutrophil count Increases SOD activity Downregulates IL-6, TNF-α and IL-1β	[206]
	(E)-Cinnamaldehyde 	Reduces neutrophil phagocytosis Increase in IL-8 secretion inhibits PMA induced NETs Hot cinnamon candies blocks NETs progression	[88]
	Beta-carotene	Anti-inflammatory activity by reducing the area of alveolitis and emphysema of lungs Reduces neutrophils and lymphocytes in broncho-	[207]

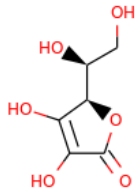
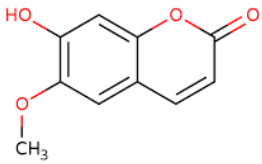
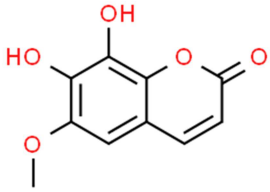
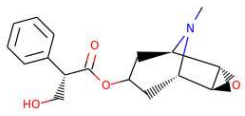
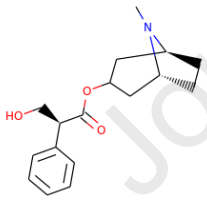
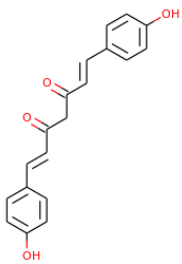
		alveolar fluid	
Withania somnifera	Withaferin A	Anti-arthritic and anti-inflammatory activities	[133]
			
	Withanolide E	Immunosuppressive effect on human B and T lymphocytes and on mice thymocytes	[133]
			
Zingiber officinale	Gingerol	Anti-oxidant property	[208]
		Anti-inflammatory effect without interfering with antigen presenting function of macrophages	[89]
		Suppresses the TNF-α production in TPA-treated female ICR-mice and rats	
		Inhibits the production of NETs formation and ROS production in response to various lupus stimuli except PMA	
	1,8-Cineol	Decreases the neutrophil chemotaxis induced by formyl-methionyl-leucyl-phenylalanine (fMLP)	[209]
		Inhibits carrageenan-induced edema and neutrophil migration	
	Zingeron	Decreases neutrophil infiltration	[210]
		Reduces neutrophil MPO activity, MPO	
Asparagus racemosus	Shatavaroside A	Anti-inflammatory effect	[211]

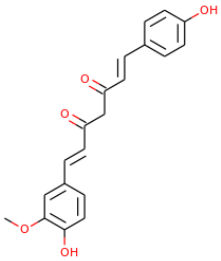
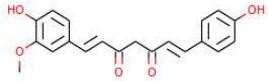
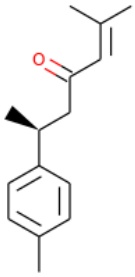
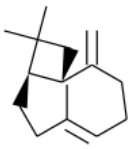
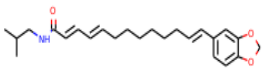
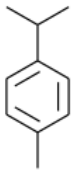
			
	Shatavaroside B	Increases phagocytosis and phagocytic index of PMN	
			
Phyllanthus niruri	Rutin	Anti-oxidant effect	[212]
			
	Quercetin	Anti-fungal, anti-inflammatory, anti-oxidant, antiseptic activities Reduces NETs production Inhibits neutrophil degranulation	[213] [214] [215]
			
	Quercitrin	Anti-inflammatory activity	[65]
			
	Astragalin	Enhances the phagocytosis, increasing macrophage count, enhancing antibodies synthesis	[65]

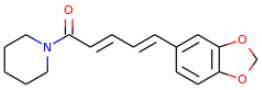
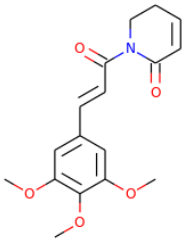
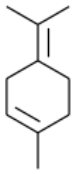
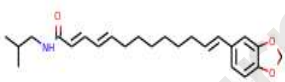
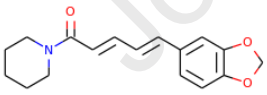
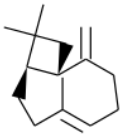
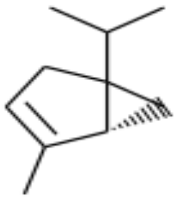
			
	p-Cymene	Antioxidant activity	[65]
			
Oscimum sanctum	Apigenin Polyphenols	Anti-inflammatory effect	[216]
			
	Catechin	Antioxidant property	[217]
			
	Isothymusin	Antioxidant activity	
			
	Isothymonin	COX-1 enzyme inhibition activity	[218]
			
	Cirsimaritin		
			
	Cirsilineol		

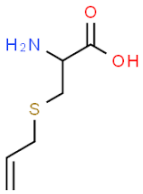
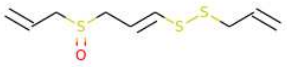
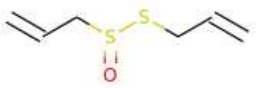
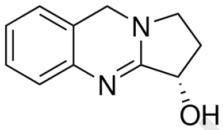
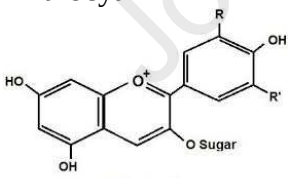
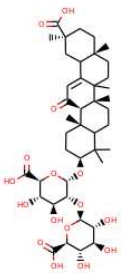
			
	Phenolic acid	Antioxidant activity	[219]
			
	Rosmarinic acid	Inhibits 97% COX-1 enzyme activity	
			
	Eugenol		
			
Andrographis paniculata	Andrographolide	Inhibits inflammatory responses in rat neutrophils	[220]
			
	14-deoxy-11,12-didehydroandrographolide	Effective against HIV virus	[221]
			

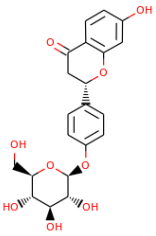
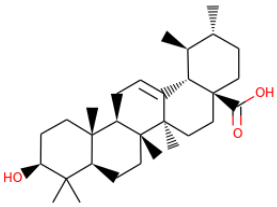
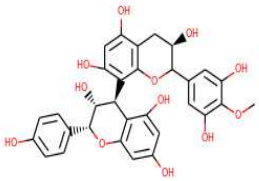
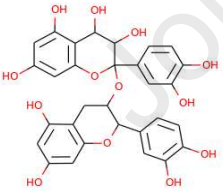
	Andrograpanin 		
	14-deoxyandrographolide 		
	5-hydroxy- 7,8-dimethoxyflavone 		
	Bis-andrographolide 		
	Diterpene 	Inhibits delayed type hypersensitivity (DTH) response to sheep red blood cells (SRBC) in mice	[222]
Emblica officinalis	l-ascorbic acid	Ascorbic acid infusion abrogates FIP induced NETs production in Vit C deficient Gulo-/- mice	[223]

			
Datura metel	Scopoletin	Inhibits IL-6, TNF-α, IL-8	[224]
			
	Fraxetin	Apoptotic inhibition of fraxetin is associated with TNF-α, IL-1β	[225]
			
	Scopolamine	Inhibits plasma and lung cytokine concentration (IL-10, IL-6 and TNF-α)	[226]
			
	Hyoscyamine	Penehyclidine hydrochloride a derivative of hyoscyamine attenuated pro-inflammatory cytokines IL-1β, IL-6 and TNF-α	[227]
			
Curcuma longa	Curcuminoids-Bisdemethoxycurcumin	Modulates IL-6, IL-8, TNF-α, TGFβ, MCP-1 Blocks cytokine release of IL-1, IL-6 and TNF-α	[228]
		Inhibits LPS induced up-regulation of IL-1β, IL-6 and TNF- α with strong down regulation of IL-8	[229]
	Demethoxycurcumin		

	 Curcumin	Regulates both pro and anti-inflammatory factors IL-6, IL-8, IL-10 and COX-2 Promotes PMN cells apoptosis Scavenges ROS	[230]
	 Turmerone	Reduces IL-1β, TNF- α, IL-6 and MCP-1 in Amyloid β stimulated microglial cells	[231]
Piper longum	 β-caryophyllene	Inhibits neutrophil migration in Cg-induced peritonitis mice model Decreases TNF-α, IFN-γ, IL-4, IL-5, IL-6	[204]
	 Guineensine	Prevents endotoxemia induced by LPS, reduction in expression of IL-1β, TNF- α and IL-6	[232]
	 p-cymene	Attenuates inflammatory cell (IL-1β, TNF- α and IL-6) number in BALF, decreases NF-κB protein level in lungs, improves SOD activity, inhibits myeloperoxidase (MPO) activity, inhibits LPS-induced neutrophils	[206]
	 Piperine	Reduces expression of IL-6, IL-1β and IgE in ovalbumin induced allergic rhinitis in mice Inhibits LPS-induced IL-1β, TNF- α, IL-6 and PGE2 production in BV2 cells	[233] [234]

			
	Hexadecane	NETs formation is triggered in neutrophils Induced IL-1β secretion in THP-1 cells. IL-1α was elevated	[235]
			
	Piperlongumine	Reduces OVA-induced airway inflammatory cell infiltration and Th2 cytokine expression	[236]
		Reduces IgE level and pro-inflammatory cytokine TNF- α, IL-6 and NF-κB activation	
	Terpinolene	Inhibits NO and reduction in O_2 production Inhibits TNF- α and IL-6	[237]
		Inhibits production of pro-inflammatory cytokines IL-1β, TNF- α and IL-6 in human keratinocyte cell line	[238]
Piper nigrum	Guineensine	Prevents endotoxemia induced by LPS, reduction in expression of IL-1β, TNF- α and IL-6	[232]
			
	Piperine	Reduces expression of IL-6, IL-1β and IgE in ovalbumin induced allergic rhinitis in mice	[233]
		Inhibits LPS-induced IL-1β, TNF- α, IL-6 and PGE2 production in BV2 cells	[234]
	β-caryophyllene	Inhibits neutrophil migration in Cg-induced peritonitis mice model	[204]
		Decreases in TNF-α, IFN-γ, IL-4, IL-5, IL-6	
	α-thujone	48.28% of α-thujone in Artemisia fukudo inhibits pro-inflammatory cytokines IL-1β, TNF- α and IL-6 in LPS induced macrophages	[239]
			
Allium sativum	Diallyl Disulfide	Suppresses pro-inflammatory cytokines TNF-α, IL-1β and IL-2, inhibits iNOS, COX-2 and NO-	[240]

		PGE2 by blocking NF-κB	
	Diallyl trisulfide 	Inhibits LPS-induced iNOS, COX-2, TNF-α and IL-1β	[241]
	Allin 	Inhibits TNF-α and IL-1β in the BALF induced by LPS. Inhibits NF-κB activation	[242]
	Ajoene 	Increases levels of INF-γ and IL-12 Partial inhibition of TNF-α	[243] [244]
	Allicin 	Reduces LPS-induced increased pro-inflammatory cytokines TNF-α, IL-1β, IL-6 and NO by HO-1 up-regulation Down-regulates TNF-α, IL-1β, IL-6 in dose dependent manner	[245] [246]
Adhatoda vasica	Vasicine 	Reduces TNF-α and IL-6	[247]
	Anthocyanin 	Inhibits TNF-α, IL-6, IL-8, IL-1β and CCL2	[248]
Glycyrrhiza glabra	Glycyrrhizin acid 	Inhibits IL-1β, IL-3, IL-5, IL-6, IL-10, IL-12 (p40), IL-12 (p70), IL-13, Eotaxin and TNF-α secreted by LPS-induced RAW264.7 cells	[197]
	Liquiritin	TNF-α, IL-1β and IL-6 were decreased in LPS-stimulates BV2 cells	[249]

			
Alstonia scholaris	Ursolic acid 	Inhibits IL-2, IL-4, IL-6 and IFN-γ. It also inhibits IL-6, IL-1β and TNF-α	[250]
Vitis vinifera	Proanthocyanidin 	Decreases mRNA expressions of IFN-γ, ICAM-1, IL-6, IL-17A, IL1β and TNF-α	[251]
	Procyanidin 	Decreases pro-inflammatory cytokines TNF-α and IL-6 in mesenteric WAT	[252]
		Inhibits TNF-α and IL-1β expression	[253]
		Suppresses production of NO, PGE_2 and ROS thus suppressing inflammation	
		Suppresses protein expression of iNOS and COX-2, inhibition of NF-κB activity through p38 downregulation