Journal of Ayurveda and Integrative Medicine 13 (2022) 100424

Contents lists available at ScienceDirect

Journal of Ayurveda and Integrative Medicine

journal homepage: http://elsevier.com/locate/jaim

Review Article

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

Manjunath B. Joshi [a], Archana Kamath [a], Aswathy S. Nair [a], Pooja Yedehali Thimmappa [a], Sitaram J. Sriranjini [b], G.G. Gangadharan [b], Kapaettu Satyamoorthy [a, *]

[a] Manipal School of Life Sciences, Manipal Academy of Higher Education, Manipal, 576104, India
[b] Ramaiah Indic Speciality Ayurveda-Restoration Hospital, MSR Nagar, Mathikere, Bengaluru, 560 054, India

ARTICLE INFO

Article history:
Received 22 July 2020
Received in revised form
8 December 2020
Accepted 9 March 2021
Available online 16 March 2021

Keywords:
Ayurveda
NETosis
Immunomodulation
Free radicals
Herbal drugs

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 have 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.

1. 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

* Corresponding author.
E-mail: ksatyamoorthy@manipal.edu
Peer review under responsibility of Transdisciplinary University, Bangalore.

https://doi.org/10.1016/j.jaim.2021.03.006

(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.

1.1. 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].

1.2. 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.

1.3. 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].

1.4. 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 [33].

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 [34]. Interestingly, IL-6R blocking antibody Tocilizumab was beneficial in reducing immune dysregulation by increasing the lymphocyte count and HLA-DR expression in response to SARS-CoV-2 [35]. Neutrophils are known to shed sIL-6Rα in response to IL-6 [36] and studies have demonstrated the abundance of IL-6 in the SARS-CoV-2–associated cytokine storm [37,38]. 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 [39]. 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 [40]. Elevated IL-1β in SARS-CoV-2 infected subjects is also known to induce NETs in aortic aneurysms and atherosclerosis [41–44]. 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 [38,31].

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 [45]. 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 [46]. Oxidant enzymes such as myeloperoxidase (MPO) are one of the key enzymes in the formation of NETs and MPO knockout mouse models failed to form intact NETs [47]. 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 [48].

1.5. 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 [49]. 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 [50]. 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.

1.6. 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 [54,76,80,83,89]. 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 [154]. 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 [155]. Bioactive molecules such as chebulinic acid and chebulagic acid showed antiviral properties against HSV-2 and HIV [55].

Aqueous extract of *P. 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 [72]. Studies have shown that *Phyllantus 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 [73]. Authors also demonstrated polyphenolic extract and gallic acid from *P. urinaria* exhibited anti-HIV-1 activities [73]. Procyanidin, a phytochemical from *Vitis vinifera*, showed anti-influenza A activity and could constrain the replication of virus at some stages of life cycle [80].

Active components of Glycyrrhiza such as glabridin, gabrin, glabrol, glabrene, hispaglabridin A, hispaglabridin B, 40-methylglabridin, and 3-hydroxyglabrol exhibited *in vitro* antimicrobial activity [156]. 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 [156]. Aqueous and methanolic extracts of *Justicia adhatoda* has been demonstrated to possess

Table 1
Charaka Samhita and Bhavaprakasha references for Ayurvedic herbs with therapeutic properties to target respiratory system along with evidences to modulate neutrophil functions [52,53].

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), Rasayana* (rejuvenation), *Bruhmana* (nourishing), *Shwasa-Kasahara* (respiratory disorders), *Shothahara* (anti-inflammation), *Krimihara* (anti-microbial), *Vishama Jwara* (intermittent fever)		a) Antimicrobial b) Immunomodulatory	[54,55,56–58]
		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: 20–80 μg/mL LPS-induced mice microglial cell	Decreases TNF-α, IL-1β, IL-6, PGE-2, COX-2	
		In vivo: 100 mg/kg, p.o. for 4 days in male Wistar rats	Increases IL-2, IL-10 and TNF-α	
		In vivo: 1 g/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), *Rasayana* (rejuvenation), *Bruhmana* (nourishing), *Shwasa-Kasahara* (respiratory disorders), *Shothahara* (anti-inflammation), *Krimihara* (anti-microbial), *Vishama Jwara* (intermittent fever)		a) Antimicrobial b) Immunomodulatory c) Antithrombotic	[54,59,60–64]
		In vitro: 500 μg/mL IB3-1 cells 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: 200 mg/kg from day 15 in male albino Wistar rats	Reduces IL-1β, IL-18 and capase-1	
		In vivo: 540 mg/kg p.o. for 7 days in albino rats of either sex by Carrageenan induced rat paw edema method	Decreases neutrophil count	
		In vivo: 5 mg/kg p.o. for 3 days, in male Swiss Albino mice	Gallic acid reduces neutrophil infiltration	
		In vitro: 1 g/kg/d for 48days, in male albino rats with indomethacin induced gastric ulceration	Triphala contains *E. officinalis* as a main ingredient. Increases the neutrophil adhesion in noise stress induced mice	
		In vitro: 20–500 μg/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	[65,66–71]
		In vitro: <5 mg/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: 20 μl; 10 mg/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: 400 mg/kg p.o. once a week for 4 weeks, male Swiss albino mice with Azoxymethane-induced colon cancer	Increases neutrophil count	
		In vivo: 10 mg/kg/d day 5–21 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	[72,73,74,75]
		In vivo: 2 μg-2 mg (w/v) i.p. *Oreochromis mossambicus* fish of either sex	Enhances neutrophil activation	
		In vitro: 1.56–25 μM, 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 (anti-microbial)		a) Antimicrobial b) Immunomodulatory c) Antithrombotic	[76,77–79]
		In vivo: 1.23 and 2.46 ml/kg p.o. for 28 days, in male Wistar rats sensitized with ovalbumin 40 mg and aluminium hydroxide 2.0 mg	*D. metel* is the major ingredient of Kanakasava. Inhibits IL-4, IL-5, IL-1β and TNF-α Reverses	

Table 1 (*continued*)

Ayurvedic herb (Botanical name)	Properties & indication as per Ayurveda	Dose/Model	Function in relation to neutrophil activity in COVID-19	Reference
			elevated neutrophil in blood & BALF	
		In vivo: 0–0.08 ml/kg SC for 10 days in Western African Dwarf bucks	Increases neutrophils counts	
Draksha *(Vitis vinifera)*	Jwara (pyrexia), Kasa-Shwasa (respiratory ailments), Swarya (voice enhancer), Raktapitta (bleeding disorders), Bruhmana (nourishing)		a) Antimicrobial b) Immunomodulatory c) Antithrombotic	[80,81,82]
		In vivo: 0.9–5.1 ng/mL, in adult male Wister rats	Decreases neutrophil migration in response to LPS	
Guduchi *(Tinospora cordifolia)*	*Tridoshahara*, *Rasayana* (rejuvenation), *Balya* (provides strength), *Agni deepana* (appetizer), *Kasa* (cough), *Jwara* (pyrexia), *Krimi* (anti-microbial).		a) Antimicrobial b) Immunomodulatory c) Antithrombotic	[83,84,85,86–88]
		In vivo: 300 mg p.o. for 8 weeks, human clinical trial	Decreases neutrophil & basophils in nasal smear	
		In vivo: 1 g/kg in 2 mL volume p.o. from day 9 –19 in Male Lewis rats adjuvant induced arthritis model	Reduces pro-inflammatory mediators IL-1β, IL-6, IL-23, TNF-α and MIP-1	
		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	*Guduchi Ghana* contains *T. cordifolia* Anti-inflammatory activity	
Haridra *(Curcuma longa)*	*Krimighni* (anti-microbial), *Kapha-pitta* hara (mitigates *kapha-pitta*) *Shirovirechana*		a) Antimicrobial b) Immunomodulatory. c) Antithrombotic	[89,90,91,92,93]
		*Ex vivo:*50 μM. Mouse colonic epithelial cells (YAMC). Intra-peritoneal macrophages from BALB/c mice	Curcumin effectively reduced LPS-stimulated chemokine secretion MIP-2, IL-1β, MIP-1α	
		In vivo: 100 μg/g in 80 μl 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: 50 mg/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-β Receptor II	
Kalamegha *(Andrographis paniculata)*	*Deepana* (appetizer), *Kapha-pitta hara* (mitigates *kapha-pitta*), *Krimighna* (anti-microbial), *Jwara* (pyrexia)		a) Antimicrobial. b) Immunomodulatory. c) Antithrombotic	[94–96]
		In vitro: 0.1–1 μM 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	[85,97–100]
		In vivo: 50–200 mg/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: 100 mg/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 integerrima)*	*Kapha-vatahara* (mitigates *kapha-vata*), *Jwara* (pyrexia), *Shwasa-Kasa* (respiratory ailments), *Aruchi* (tastelessness), *Vami* (vomiting)		a) Antimicrobial. b) Immunomodulatory	[101–103]
		In vivo: 7.5–30 mg/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)		a) Antimicrobial. b) Immunomodulatory. c) Antithrombotic	[104,105–108]
		In vitro: Endothelial cell monolayers from human umbilical endothelial cells	Inhibits neutrophil migration	
		In vivo: 80 mg/kg p.o. for 4 weeks. *Dermatophagoides pteronyssinus* (Der p) induced allergic asthma mice model	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	

(*continued on next page*)

Table 1 (*continued*)

Ayurvedic herb (Botanical name)	Properties & indication as per Ayurveda	Dose/Model	Function in relation to neutrophil activity in COVID-19	Reference
Maricha *(Piper nigrum)*	*Deepana, Krimighna, Shirovirechana, Kapha-vatahara* (mitigates Kapha-vata), Deepana (appetizer), *Shwasa* (respiratory disease), *Shoola* (pain), *Krimi* (microbes)	*In vitro:* 50–100 μg/ml in BALB/c mice spleenocytes. *In vivo:* 200 mg/kg p.o. day 15–26 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	[109,110–112]
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 ailments), *Jeerna Jwara* (Chronic fever)	*In vitro:* 17.5 μg/mL. Human endothelial cells *In vivo:* 10–100 mg/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	[113–115]
Pushkara *(Inula racemosa)*	*Kapha-vatahara* (mitigates *kapha-vata*), *Jwara* (fever), *Shotha* (anti-inflammatory) *Kasa-shwasa* (respiratory ailments), *Aruchi* (tastelessness)	*In vivo:* 500 mg/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.	[116–120]
Saptaparna *(Alstonia scholaris)*	*Shirovirechana, Shleshma-vata hara* (mitigates *kapha-vata hara*), *Shwasahara*	*In vivo:* 50–200 mg/kg in BALB/c mice *In vitro:* 1–25 μg/mL in human neutrophils *In vivo:* 10–50 mg/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	[121–123]
Shatavari *(Asparagus racemosus)*	*Balya* (provides strength), *Vata pitta hara* (mitigates *vata-pitta*), *Agni pustida* (increases digestive power), *Rasayana* (rejuvenation), *Shothajit* (anti-inflammatory)	*In vivo:* 100 mg/kg/d p.o. 15 days in Swiss albino mice with cyclophosphamide induced neutropenia *In vivo* 200 mg/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	[124,125,126]
Shati *(Hedychium spicatum)*	*Shwasahara, Kapha-vatahara* (mitigates *Kapha-vata*), *Shothahara* (anti-inflammatory), *Shwasa-Kasa* (respiratory ailments), *Shoolahara* (analgesic)	*In vivo:* 200–500 mg/kg p.o. for 15 days in Swiss albino mice and albino rats. Ovalbumin induced allergic asthma	a) Antimicrobial. b) Immunomodulatory Increases neutrophil count	[127,128]
Shunthi *(Zingiber officinale)*	*Kapha-vatahara* (mitigates *Kaphavata*), *Ruchya* (enhances taste), *Pachana* (digestion), *Swarya* (enhances voice), *Shwasa-Kasa* (respiratory ailments), *Shoola* (pain), *Shopha* (inflammation)	*In vivo:* 500 mg/kg and 720 mg/kg i.p. in Male BALB/c mice *In vivo*: 45–720 mg/kg i.p. day 7 and 8 in NOD mice and C57BL/6 mice Ovalbumin induced	a) Antimicrobial. b) Immunomodulatory. c) Antithrombotic Decreases neutrophils in BALF. Lowers IL-4 and IL-5 Reduces IL-5 and IL-4	[129,130,131,132]
Talisapatra *(Abies webbiana)*	*Shwasa-Kasa* (respiratory ailments), *Kapha anila apaha* (mitigates kaphavata), *Aruchi* (tastelessness), *Vahnimandya* (decreased appetite)		a) Antimicrobial	[133]
Tulasi (*Ocimum sanctum*)	*Shwasahara Kapha-vatajit* (mitigates kaphavata), *Deepana* (appetizer), *Bhutagni* (anti-microbial), *Kasa-Shwasa* (respiratory ailments)	*In vivo:* 100 mg/kg i.p. for 45 days in Wistar strain male albino rats *In vivo:* 250 mg/kg p.o. for 20 days in Albino Wister rats. *In vitro:* 25–500 μg/ml in Spleenocytes *In vivo:* 250 mg/kg for 20 days in Wistar albino rats of either sex. Excision model of wound repair *In vivo:* 850 mg/kg p.o. for 15 days in Swiss albino mice	a) Antimicrobial. b) Immunomodulatory. c) Antithrombotic Enhances phagocytic activity of neutrophil Enhances IL-2 Up regulates TNF-α production Elevates IL-2, IL-4, TNF-α and IFN- γ. Reduces IL-1β and NF-kB levels	[134,135–139]
	Anila pitta hrut (mitigates *vata pitta*), *Aruchi* (tastelessness), *Pinasa* (rhinitis),		a) Antimicrobial. b) Immunomodulatory	[140–142]

Table 1 (*continued*)

Ayurvedic herb (Botanical name)	Properties & indication as per Ayurveda	Dose/Model	Function in relation to neutrophil activity in COVID-19	Reference
Twak (*Cinnamomum zeylanicum*)	*Kasa* (respiratory ailments), *Krimi* (anti-microbial)	*In vivo:* 10–100 mg/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	[143,144–147]
		In vivo: 10 gm/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: 400 mg/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) AntithromboticAntitussive, expectorant, antimicrobial, antiviral, anti-oxidant, anti-inflammatory, immune –modulatory activity	[148,149,150–153]
		In vitro: 25–100 μg/mL in RAW 264.7 macrophages stimulated with LPS	Inhibits LPS-induced TNF-α, IL-1β, IL-6 production	
		In vitro: 50–200 μg/ml in LPS-stimulated mouse endometrial epithelial cells	Glycyrrhizin inhibits LPS-induced TNF-α, IL-1β, NO & PGE_2 production	
		In vitro: 200, 40, 8 mg/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: 50–100 mg/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.

antiviral activity against influenza virus upon inhibiting Hemagglutination (HA) [143].

A. 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 [104]. Interestingly, independent studies have shown that above mentioned herbs such as *T. chebula* [54], *P. niruri* [157], *V. vinifera* [80], *G. glabra* [148], *J. adhatoda* [143] and *A. sativum* [158] significantly modulated neutrophil functions in disease conditions.

1.7. 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 [65,84,134]. 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 [124]. 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 [129,159]. 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 [160]. Piper species have been studied extensively for anti-bacterial, anti-mutagenic, anti-tumor, anti-diabetic, antioxidant and anti-inflammatory properties [161,162]. 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* [109]. Herbs used in Ayurveda system such as Abhaya *(T. chebula),* Draksha *(V. vinifera),* Kantakari *(Solamun xanthocarpum),* Pushkara *(Inula racemosa)*, Shati *(Hedychium spicatum)*, Talisapatra *(Abies webbiana)* and Karkatashringi (*P. integerrima)* has also been shown to possess

antioxidant and immunomodulatory properties and significantly modulate neutrophil activity as indicated in Table no 1 and Fig. 1.

1.8. 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 antioxidant and free radical scavenging activities. Antioxidant enzymes such as catalase, SOD and GP_X increased upon the treatment of *W. somnifera* in rat brain [221]. 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 [222]. Withanolide showed anti-inflammatory activity by suppressing superoxide anion generation and release of elastase in neutrophils stimulated by fMLP [223]. 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 [224]. 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 [225]. 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 [59]. *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 [48]. 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 [226]. Influence of quercetin hydrate on reducing NETs formation was also demonstrated in bovine neutrophils [227]. Andrographolide is one of the bioactive molecules found in *A. paniculata*. Maria et al. (2013) reviewed several studies and proposed underlying mechanisms for the anti-inflammatory

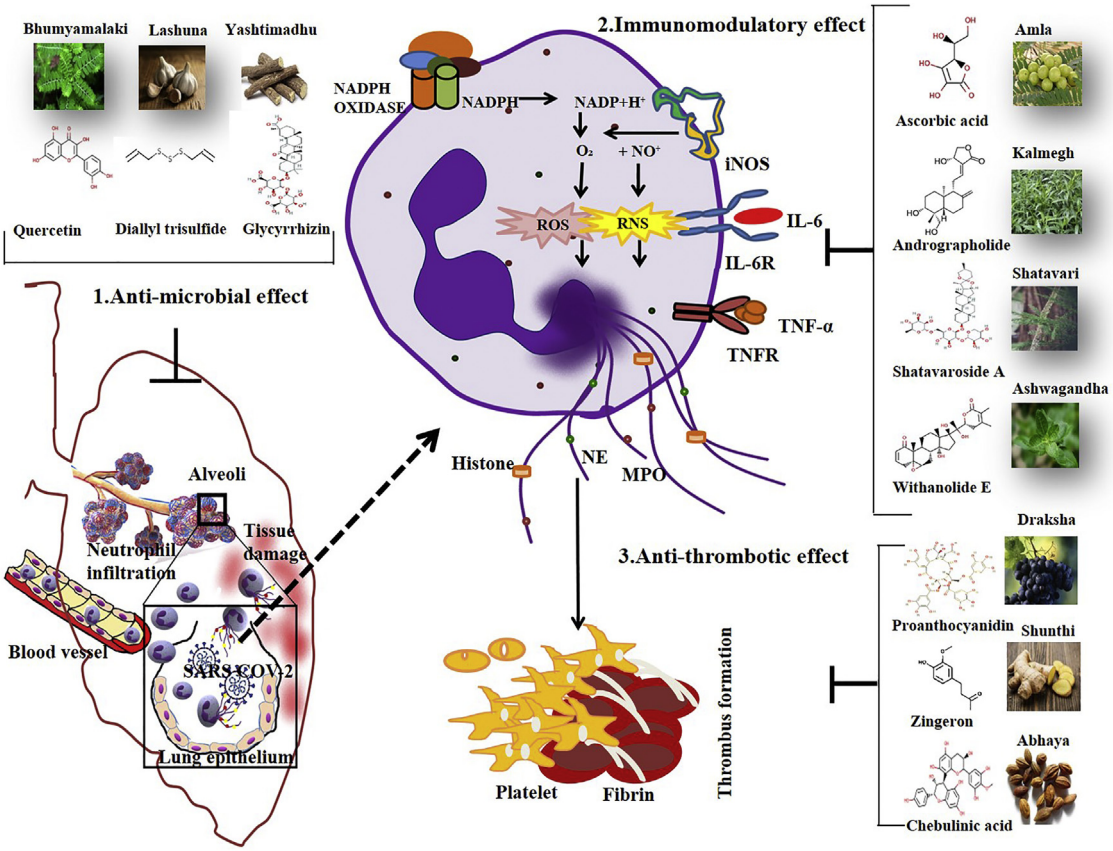
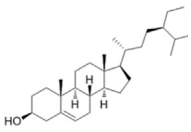
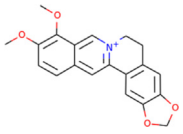
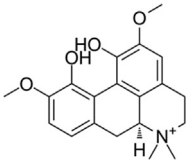
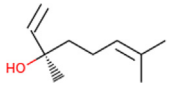
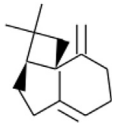
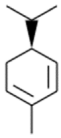
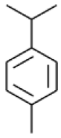
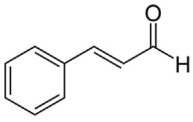


Fig. 1. Influence of Ayurvedic herbs in modulating neutrophil functions and its potential role in COVID-19 management. Examples of representative Ayurvedic herbs containing bioactive molecules might act as a) anti-viral, b) inhibit formation of NETs by reducing cytokine storm due to the excess release of pro-inflammatory mediators such as IL-6, IL-10, TNF-α, c) reduce NETs formation to decrease platelet aggregation and thrombosis.

Table 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 Increases neutrophils count Inhibits secretion of TNF-α, IL-1β, IL-6, IL-8 Reduces NLRP3 and capase-1	[163] [164]
	Berberine 	Anti-inflammatory Downregulates MCP-1, IL-6, TNF-α Attenuates the inflammation in the air way by inhibiting neutrophil infiltration	[165]. [166]
	Magnoflorine 	Anti-inflammatory, immuno-modulatory, antioxidant activity	[167]
Cinnamomum zeylanicum	(−)-Linalool 	Inhibits eosinophil numbers, Th2 cytokines and IgE levels Prevents the influx of inflammatory cells and hyper secretion of mucus	[168]
	Beta-caryophyllene 	Inhibits of neutrophil migration in Cg-induced peritonitis mice model Decreases in TNF-α, IFN-γ, IL-4, IL-5, IL-6	[169]
	(+)-alpha-phellandrene 	Prevents induction of Neutrophil accumulation Inhibits TNF-α and IL-6	[170]
	p-cymene 	Reduces total leukocyte and neutrophil count Increases SOD activity. Downregulates IL-6, TNF-α and IL-1β	[171]
	(E)-Cinnamaldehyde 	Reduces neutrophil phagocytosis Increase in IL-8 secretion inhibits PMA induced NETs Hot cinnamon candies blocks NETs progression	[172] [173]

(*continued on next page*)

Table 2 (*continued*)

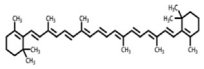
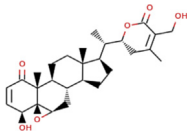
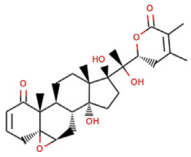
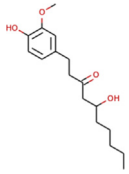
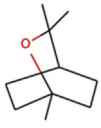
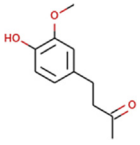
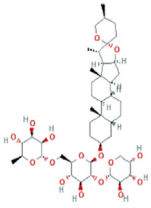
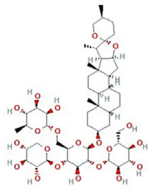
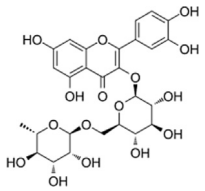
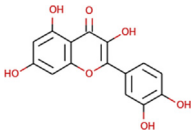
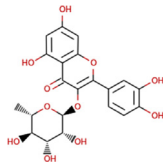
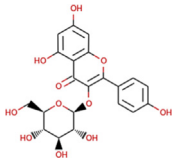
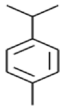
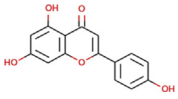
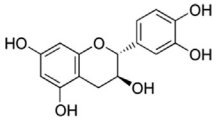
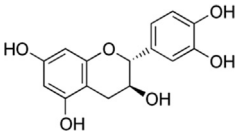
Name of the herb	Phytochemical name	Function	Reference
	Beta-carotene 	Anti-inflammatory activity by reducing the area of alveolitis and emphysema of lungs. Reduces neutrophils and lymphocytes in broncho-alveolar fluid	
Withania somnifera	Withaferin A 	Anti-arthritic and anti-inflammatory activities	[67]
	<		
	Withanolide E 	Immunosuppressive effect on human B and T lymphocytes and on mice thymocytes	[67]
Zingiber officinale	Gingerol 	Anti-oxidant property. Anti-inflammatory effect without interfering with antigen presenting function of macrophages 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	[174]. [175]
	1,8-Cineol 	Decreases the neutrophil chemotaxis induced by formyl-methionyl-leucyl-phenylalanine (fMLP) Inhibits carrageenan-induced edema and neutrophil migration	[176]
	Zingeron 	Decreases neutrophil infiltration. Reduces neutrophil MPO activity, MPO	[177]
Asparagus racemosus	Shatavaroside A 	Anti-inflammatory effect.	[178]
	Shatavaroside B 	Increases phagocytosis and phagocytic index of PMN	

Table 2 (*continued*)

Name of the herb	Phytochemical name	Function	Reference
Phyllanthus niruri	Rutin 	Anti-oxidant effect	[179]
	Quercetin 	Anti-fungal, anti-inflammatory, anti-oxidant, antiseptic activities Reduces NETs production Inhibits neutrophil degranulation	[180] [181] [182]
	Quercitrin 	Anti-inflammatory activity	[157]
	Astragalin 	Enhances the phagocytosis, increasing macrophage count, enhancing antibodies synthesis	[157]
	p-Cymene 	Antioxidant activity	[157]
Oscimum sanctum	Apigenin Polyphenols 	Anti-inflammatory effect	[183]
	Catechin 	Antioxidant property	[184]
	Isothymusin 	Antioxidant activity.	[185]
	Isothymonin	COX-1 enzyme inhibition activity	

(*continued on next page*)

Table 2 (*continued*)

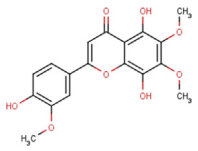
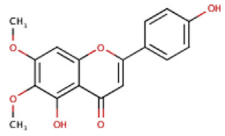
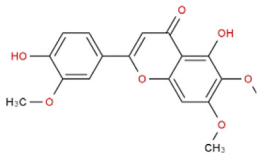
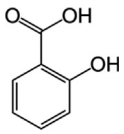
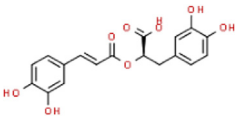
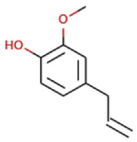
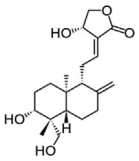
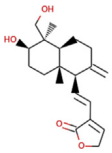
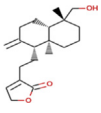
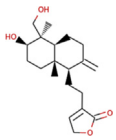
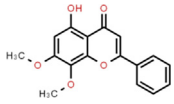
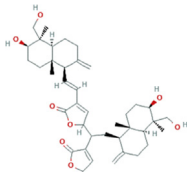
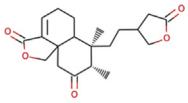
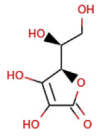
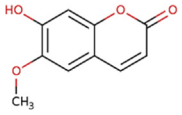
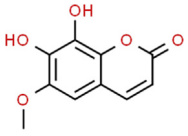
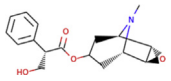
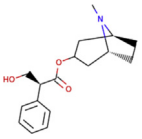
Name of the herb	Phytochemical name	Function	Reference
	 Cirsimaritin		
	 Cirsilineol		
	 Phenolic acid	Antioxidant activity.	[186]
	 Rosmarinic acid	Inhibits 97% COX-1 enzyme activity	
	 Eugenol		
			
Andrographis paniculata	Andrographolide	Inhibits inflammatory responses in rat neutrophils	[187]
	 14-deoxy-11,12-didehydroandrographolide	Effective against HIV virus	[188]
	 Andrograpanin		
	 14- deoxyandrographolide		

Table 2 (*continued*)

Name of the herb	Phytochemical name	Function	Reference
			
	. 5-hydroxy- 7,8- dimethoxyflavone 		
	. Bis-andrographolide 		
	Diterpene 	Inhibits delayed type hypersensitivity (DTH) response to sheep red blood cells (SRBC) in mice	[189]
Emblica officinalis	L-ascorbic acid 	Ascorbic acid infusion abrogates FIP induced NETs production in Vit C deficient Gulo−/− mice	[190]
Datura metel	Scopoletin 	Inhibits IL-6, TNF-α, IL-8	[191]
	Fraxetin 	Apoptotic inhibition of fraxetin is associated with TNF-α, IL-1β	[192]
	Scopolamine 	Inhibits plasma and lung cytokine concentration (IL-10, IL-6 and TNF-α)	[193]
	Hyoscyamine 	Penehyclidine hydrochloride a derivative of hyoscyamine attenuated pro-inflammatory cytokines IL-1β, IL-6 and TNF-α	[194]

(*continued on next page*)

Table 2 (*continued*)

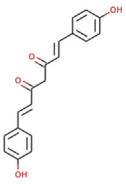
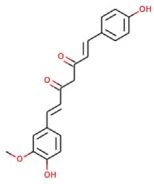
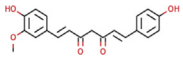
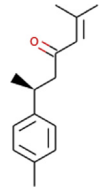
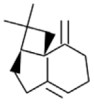
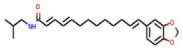
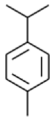
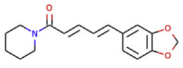
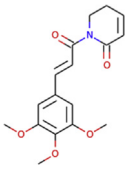
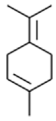
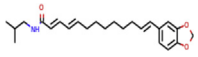
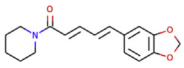
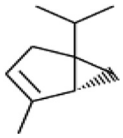
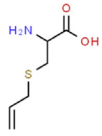
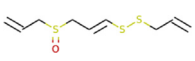
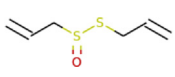
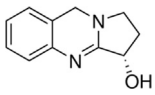
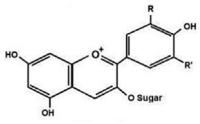
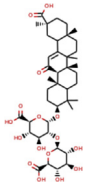
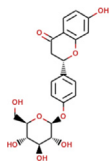
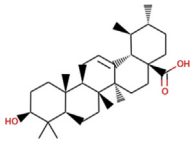
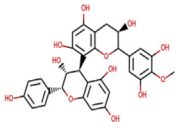
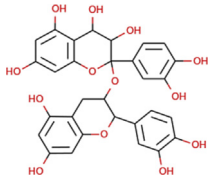
Name of the herb	Phytochemical name	Function	Reference
Curcuma longa	Curcuminoids-Bisdemethoxycurcumin 	Modulates IL-6, IL-8, TNF-α, TGFβ, MCP-1 Blocks cytokine release of IL-1, IL-6 and TNF-α Inhibits LPS induced up-regulation of IL-1β, IL-6 and TNF- α with strong down regulation of IL-8	[195]. [196] [197]
	Demethoxycurcumin 		
	Curcumin 	Regulates both pro and anti-inflammatory factors IL-6, IL-8, IL-10 and COX-2 Promotes PMN cells apoptosis Scavenges ROS	[196]
	Turmerone 	Reduces IL-1β, TNF- α, IL-6 and MCP-1 in Amyloid β stimulated microglial cells	[198]
Piper longum	β-caryophyllene 	Inhibits neutrophil migration in Cg-induced peritonitis mice model. Decreases TNF-α, IFN-γ, IL-4, IL-5, IL-6	[169]
	Guineensine 	Prevents endotoxemia induced by LPS, reduction in expression of IL-1β, TNF- α and IL-6	[199]
	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	[171]
	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	[200] [201]
	Hexadecane	NETs formation is triggered in neutrophils Induced IL-1β secretion in THP-1 cells. IL-1α was elevated	[202]

Table 2 (*continued*)

Name of the herb	Phytochemical name	Function	Reference
	Piperlongumine 	Reduces OVA-induced airway inflammatory cell infiltration and Th2 cytokine expression. Reduces IgE level and pro-inflammatory cytokine TNF- α, IL-6 and NF-κB activation	[203]
	Terpinolene 	Inhibits NO and reduction in O_2 production Inhibits TNF- α and IL-6. Inhibits production of pro-inflammatory cytokines IL-1β, TNF- α and IL-6 in human keratinocyte cell line	[204]. [205]
Piper nigrum	Guineensine 	Prevents endotoxemia induced by LPS, reduction in expression of IL-1β, TNF- α and IL-6	[199]
	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	[200]. [201]
	β-caryophyllene 	Inhibits neutrophil migration in Cg-induced peritonitis mice model. Decreases in TNF-α, IFN-γ, IL-4, IL-5, IL-6	[169]
	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	[206]
Allium sativum	Diallyl Disulfide 	Suppresses pro-inflammatory cytokines TNF-α, IL-1β and IL-2, inhibits iNOS, COX-2 and NO-PGE2 by blocking NF-κB	[207]
	Diallyl trisulfide 	Inhibits LPS-induced iNOS, COX-2, TNF-α and IL-1β	[208]
	Allin 	Inhibits TNF-α and IL-1β in the BALF induced by LPS. Inhibits NF-κB activation	[209]
	Ajoene 	Increases levels of INF-γ and IL-12. Partial inhibition of TNF-α	[210]. [211]
	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	[212]. [213]

(*continued on next page*)

Table 2 (*continued*)

Name of the herb	Phytochemical name	Function	Reference
Adhatoda vasica	Vasicine 	Reduces TNF-α and IL-6	[214]
	Anthocyanin 	Inhibits TNF-α, IL-6, IL-8, IL-1β and CCL2	[215]
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	[153]
	Liquiritin 	TNF-α, IL-1β and IL-6 were decreased in LPS-stimulates BV2 cells	[216]
Alstonia scholaris	Ursolic acid 	Inhibits IL-2, IL-4, IL-6 and IFN-γ. It also inhibits IL-6, IL-1β and TNF-α	[217]
Vitis vinifera	Proanthocyanidin 	Decreases mRNA expressions of IFN-γ, ICAM-1, IL-6, IL-17A, IL1β and TNF-α.	[218]
	Procyanidin 	Decreases pro-inflammatory cytokines TNF-α and IL-6 in mesenteric WAT. Inhibits TNF-α and IL-1β expression. 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	[219] [220]

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 [228]. 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 [229]. Immunostaining of murine rheumatoid arthritis ankle showed increased PAD4 and citrullinated histone levels and further, andrographolide treatment significantly reduced these components of NETs [65]. 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 [172]. Authors demonstrated that cinnamaldehyde decreased extracellular DNA by fluorimetry and immunofluorescence [134]. In clinical models of lupus and anti-phospholipid 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 [175]. 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 [230]. 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 [231].

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 [232]. 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 [233]. 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 [90]. 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 [234]. Curcumin regulated immune response upon reducing synthesis of local inflammatory mediators *in vitro* and in mice infected with Influenza A virus [235]. 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-β 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 [91,236].

1.9. 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 [237]. 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 [238]. 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 [239]. 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 [240]. 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 [241]. NETs formation is also associated with release of metalloproteinase [242]. 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 [243]. Heinemann et al. (2016) showed the NETs formation in response to viable *S. aureaus* in hypoxic conditions [244]. 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 [245].

1.10. 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 [246]. 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 [247]. 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.

1.11. 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 [248]. On the other hand, recent data indicate COVID-19 pathogenesis is significantly

associated with thrombotic microangiopathy *via* platelet/NETs/thrombin axis [249,250]. Multifaceted role of neutrophils in the pathogenesis of stroke has been demonstrated and targeting neutrophils showed ameliorated stroke progression [251]. 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 [252]. In a transient middle cerebral artery occlusion model for stroke, administration of DNase I and neutralizing antibodies against histone led to smaller infracts [253]. 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 [254]. 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 [255].

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 *P. urinaria* containing corilagin prolonged occlusion time of carotid artery, reduced thrombus and decreased platelet–neutrophil interaction [74]. *V. 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 [81]. Methanolic extracts of *Solanum xanthocarpum* and *T. cordifolia* showed anti-thrombotic activity by significantly inhibiting thrombin induced platelet aggregation [85]. 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 [130]. 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 [149]. Interestingly, independent studies have shown Phyllantus [157], Vitis [82], Ginger [175] and glycyrrhiza [148] 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.

2. 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, Datura, Draksha, Guduchi, Haridra, Kalmegha, Kantakari, Lashuna, Shunthi and Tulasi exhibiting all these properties and hence, we suggest Ayurvedic preparations from these might be beneficial for the management of the COVID-19. However, Ayurveda also describes a personalized medicine strategy based on Prakirti and Tridoshas and hence, integration of may be necessary towards effective strategies to combat the disease.

Source of Funding

Authors gratefully acknowledge Centre for Ayurvedic Biology, MAHE, Science and Engineering Research Board (SERB), Department of Science and Technology (DST), Government of India for the support.

Conflict of interest

None.

Acknowledgements

We gratefully acknowledge Centre for Ayurvedic Biology, MAHE, Science and Engineering Research Board (SERB), Department of Science and Technology (DST), Government of India and MAHE for the support and encouragement.

References

[1] WHO Coronavirus Disease (COVID-19) dashboard | WHO coronavirus disease (COVID-19) dashboard n.d.
[2] Beltrán-García J, Osca-Verdegal R, Pallardó FV, Ferreres J, Rodríguez M, Mulet S, et al. Oxidative stress and inflammation in COVID-19-associated sepsis: the potential role of anti-oxidant therapy in avoiding disease progression. Antioxidants 2020;9:936.
[3] Mortaz E, Tabarsi P, Varahram M, Folkerts G, Adcock IM. The immune response and immunopathology of COVID-19. Front Immunol 2020;11:2037.
[4] Barnes BJ, Adrover JM, Baxter-Stoltzfus A, Borczuk A, Cools-Lartigue J, Crawford JM, et al. Targeting potential drivers of COVID-19: neutrophil extracellular traps. J Exp Med 2020;217:e20200652.
[5] Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, et al. Neutrophil extracellular traps kill bacteria. Science 2004;303:1532–5.
[6] Keshari RS, Jyoti A, Kumar S, Dubey M, Verma A, Srinag BS, et al. Neutrophil extracellular traps contain mitochondrial as well as nuclear DNA and exhibit inflammatory potential. Cytometry 2012;81:238–47. A.
[7] Urban CF, Ermert D, Schmid M, Abu-Abed U, Goosmann C, Nacken W, et al. Neutrophil extracellular traps contain calprotectin, a cytosolic protein complex involved in host defense against Candida albicans. PLoS Pathog 2009;5:e1000639.
[8] Papayannopoulos V. Neutrophil extracellular traps in immunity and disease. Nat Rev Immunol 2018;18:134–47.
[9] Saitoh T, Komano J, Saitoh Y, Misawa T, Takahama M, Kozaki T, et al. Neutrophil extracellular traps mediate a host defense response to human immunodeficiency virus-1. Cell Host Microbe 2012;12:109-16.
[10] Funchal GA, Jaeger N, Czepielewski RS, Machado MS, Muraro SP, Stein RT, et al. Respiratory syncytial virus fusion protein promotes TLR-4–dependent neutrophil extracellular trap formation by human neutrophils. PloS One 2015;10:e0124082.
[11] Raftery MJ, Lalwani P, Krautkrämer E, Peters T, Scharffetter-Kochanek K, Krüger R, et al. β2 integrin mediates hantavirus-induced release of neutrophil extracellular traps. J Exp Med 2014;211:1485–97.

[12] Moorthy AN, Narasaraju T, Rai P, Perumalsamy R, Tan KB, Wang S, et al. In vivo and in vitro studies on the roles of neutrophil extracellular traps during secondary pneumococcal pneumonia after primary pulmonary influenza infection. Front Immunol 2013;4:56.
[13] Schönrich G, Raftery MJ. Neutrophil extracellular traps go viral. Front Immunol 2016;7:366.
[14] Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020;71:762–8. ciaa248.
[15] Zeng F, Li L, Zeng J, Deng Y, Huang H, Chen B, et al. Can we predict the severity of COVID-19 with a routine blood test? Pol Arch Intern Med 2020;130:400–6.
[16] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in wuhan, China. J Am Med Assoc 2020;323:1061–9.
[17] Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, et al. [A pathological report of three COVID-19 cases by minimally invasive autopsies]. Chin J Pathol 2020;49:E009.
[18] Jorch SK, Kubes P. An emerging role for neutrophil extracellular traps in noninfectious disease. Nat Med 2017;23:279–87.
[19] Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JC, Fogerty AE, Waheed A, et al. COVID and coagulation: bleeding and thrombotic manifestations of SARS-CoV2 infection. Blood 2020;136:489–500.
[20] Han H, Yang L, Liu R, Liu F, Wu K, Li J, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med 2020;58:1116–20.
[21] Boccia M, Aronne L, Celia B, Mazzeo G, Ceparano M, D'Agnano V, et al. COVID-19 and coagulative axis: review of emerging aspects in a novel disease. Monaldi Arch Chest Dis 2020;90.
[22] Zuo Y, Yalavarthi S, Shi H, Gockman K, Zuo M, Madison JA, et al. Neutrophil extracellular traps in COVID-19. JCI Insight 2020;5:e138999.
[23] Caudrillier A, Kessenbrock K, Gilliss BM, Nguyen JX, Marques MB, Monestier M, et al. Platelets induce neutrophil extracellular traps in transfusion-related acute lung injury. J Clin Invest 2012;122:2661–71.
[24] Adrover JM, Aroca-Crevillén A, Crainiciuc G, Ostos F, Rojas-Vega Y, Rubio-Ponce A, et al. Programmed 'disarming' of the neutrophil proteome reduces the magnitude of inflammation. Nat Immunol 2020;21:135–44.
[25] Bendib I, De Chaisemartin L, Granger V, Schlemmer F, Maitre B, Hüe S, et al. Neutrophil extracellular traps are elevated in patients with pneumonia-related acute respiratory distress syndrome. Anesthesiology 2019;130:581–91.
[26] Ebrahimi F, Giaglis S, Hahn S, Blum CA, Baumgartner C, Kutz A, et al. Markers of neutrophil extracellular traps predict adverse outcome in community-acquired pneumonia: secondary analysis of a randomised controlled trial. Eur Respir J 2018;51.
[27] Mikacenic C, Moore R, Dmyterko V, West TE, Altemeier WA, Liles WC, et al. Neutrophil extracellular traps (NETs) are increased in the alveolar spaces of patients with ventilator-associated pneumonia. Crit Care 2018;22:358.
[28] Lv X, Wen T, Song J, Xie D, Wu L, Jiang X, et al. Extracellular histones are clinically relevant mediators in the pathogenesis of acute respiratory distress syndrome. Respir Res 2017;18:165.
[29] Narasaraju T, Yang E, Samy RP, Ng HH, Poh WP, Liew AA, et al. Excessive neutrophils and neutrophil extracellular traps contribute to acute lung injury of influenza pneumonitis. Am J Pathol 2011;179:199–210.
[30] Manzenreiter R, Kienberger F, Marcos V, Schilcher K, Krautgartner WD, Obermayer A, et al. Ultrastructural characterization of cystic fibrosis sputum using atomic force and scanning electron microscopy. J Cyst Fibros 2012;11:84–92.
[31] Fox SE, Akmatbekov A, Harbert JL, Li G, Brown JQ, Heide RS Vander. Pulmonary and cardiac pathology in covid-19: the first autopsy series from new orleans. MedRxiv 2020:PPR149850.
[32] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033–4.
[33] Keshari RS, Jyoti A, Dubey M, Kothari N, Kohli M, Bogra J, et al. Cytokines induced neutrophil extracellular traps formation: implication for the inflammatory disease condition. PloS One 2012;7:e48111.
[34] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46:846–8.
[35] Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe 2020;27:992–1000.
[36] Marin V, Montero-Julian F, Grès S, Bongrand P, Farnarier C, Kaplanski G. Chemotactic agents induce IL-6Rα shedding from polymorphonuclear cells: involvement of a metalloproteinase of the TNF-α-converting enzyme (TACE) type. Eur J Immunol 2002;32:2965–70.
[37] Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: an emerging target of JAK2 inhibitor Fedratinib. J Microbiol Immunol Infect 2020;53:368-70.
[38] Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the experience of clinical immunologists from China. Clin Immunol 2020;214:108393.
[39] Joshi MB, Lad A, Bharath Prasad AS, Balakrishnan A, Ramachandra L, Satyamoorthy K. High glucose modulates IL-6 mediated immune homeostasis through impeding neutrophil extracellular trap formation. FEBS Lett 2013;587:2241–6.
[40] Gupta AK, Joshi MB, Philippova M, Erne P, Hasler P, Hahn S, et al. Activated endothelial cells induce neutrophil extracellular traps and are susceptible to NETosis-mediated cell death. FEBS Lett 2010;584:3193–7.
[41] Kahlenberg JM, Carmona-Rivera C, Smith CK, Kaplan MJ. Neutrophil extracellular trap–associated protein activation of the NLRP3 inflammasome is enhanced in lupus macrophages. J Immunol 2013;190:1217–26.
[42] Meher AK, Spinosa M, Davis JP, Pope N, Laubach VE, Su G, et al. Novel role of IL (Interleukin)-1β in neutrophil extracellular trap formation and abdominal aortic aneurysms. Arterioscler Thromb Vasc Biol 2018;38:843–53.
[43] Sil P, Wicklum H, Surell C, Rada B. Macrophage-derived IL-1β enhances monosodium urate crystal-triggered NET formation. Inflamm Res 2017;66:227–37.
[44] Warnatsch A, Ioannou M, Wang Q, Papayannopoulos V. Neutrophil extracellular traps license macrophages for cytokine production in atherosclerosis. Science 2015;349:316–20. 80-.
[45] Song EK, Jaishankar GB, Saleh H, Jithpratuck W, Sahni R, Krishnaswamy G. Chronic granulomatous disease: a review of the infectious and inflammatory complications. Clin Mol Allergy 2011;9:1–14.
[46] Douda DN, Khan MA, Grasemann H, Palaniyar N. SK3 channel and mitochondrial ROS mediate NADPH oxidase-independent NETosis induced by calcium influx. Proc Natl Acad Sci U S A 2015;112:2817–22.
[47] Papayannopoulos V, Metzler KD, Hakkim A, Zychlinsky A. Neutrophil elastase and myeloperoxidase regulate the formation of neutrophil extracellular traps. J Cell Biol 2010;191:677-91.
[48] Kirchner T, Hermann E, Möller S, Klinger M, Solbach W, Laskay T, et al. Flavonoids and 5-aminosalicylic acid inhibit the formation of neutrophil extracellular traps. Mediat Inflamm 2013;2013:14.
[49] Tillu G, Chaturvedi S, Chopra A, Patwardhan B. Public health approach of Ayurveda and yoga for COVID-19 prophylaxis. J Alternative Compl Med 2020;26:360–4.
[50] Acharya Yadavji Trikamji, Acharya Narayana Ram, editors. Sushruta Samhita of sushruta, nidanasthana; kustha nidana: chapter 5, verse 33-34. 7th ed. Varanasi: Chaukhambha Orientalia; 2002. p. 289.
[51] P R, Kataria S, Pm U, M P, Nampoothiri V, Sharma P, et al. Ayurvedic clinical profile of COVID-19 – a preliminary report. J Ayurveda Integr Med 2020. S0975–9476.[51a] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033–4.
[52] Acharya Yadavji Trikamji, editor. Charaka Samhita of agnivesha, sootrasthana; shadvirechana ashtashritiya adhyaya: chapter 4, verse 9-13. Varanasi: Chaukhambha Surabharati Prakashan; 2000. p. 32–4 (reprint).
[53] Mishra Brahma Sankara, editor. Bhavaprakasha – vidyotini Hindi commentary of bhavamishra. 12th ed.vol. 209. Varanasi: Chaukhambha Sanskrit Bhawan; 2018.
[54] Srikumar R, Jeya Parthasarathy N, Sheela Devi R. Immunomodulatory activity of triphala on neutrophil functions. Biol Pharm Bull 2005;28:1398–403.
[55] Kolla JN, Kulkarni NM, Kura RR, Theepireddy SKR. Terminalia chebula Retz. – an important medicinal plant. Herba Pol 2018;63:45–56.
[56] Seo JB, Jeong JY, Park JY, Jun EM, Lee SI, Choe SS, et al. Anti-arthritic and analgesic effect of NDI10218, a standardized extract of Terminalia chebula, on arthritis and pain model. Biomol Ther 2012;20:104–12.
[57] Rahimi VB, Askari VR, Shirazinia R, Soheili-Far S, Askari N, Rahmanian-Devin P, et al. Protective effects of hydro-ethanolic extract of Terminalia chebula on primary microglia cells and their polarization (M(1)/M(2) balance). Mult Scler Relat Disord 2018;25:5–13.
[58] Aher VD, Kumar A, Wahi. Immunomodulatory effect of alcoholic extract of Terminalia chebula ripe fruits. J Pharmaceut Sci Res 2010;10:567–75.
[59] Nicolis E, Lampronti I, Dechecchi MC, Borgatti M, Tamanini A, Bianchi N, et al. Pyrogallol, an active compound from the medicinal plant Emblica officinalis, regulates expression of pro-inflammatory genes in bronchial epithelial cells. Int Immunopharm 2008;8. 1672-80.
[60] Hasan MR, Islam MN, Islam MR. Phytochemistry, pharmacological activities and traditional uses of Emblica officinalis: a review. Int Curr Pharmaceut J 2016;5:14–21.
[61] Aruna V, Soundharya R, Amruthavalli G, Gayathri R. Muco-constriction: a ray of promise from medicinal plants. J Drug Deliv Therapeut 2019;9:180–2.
[62] Santoshkumar J, Devarmani MS, Sajjanar M. Original Article A study of Anti-inflammatory activity of fruit of. Med Innov 2013;2:17–25.
[63] Chatterjee A, Chatterjee S, Biswas A, Bhattacharya S, Chattopadhyay S, Bandyopadhyay SK. Gallic acid enriched fraction of *Phyllanthus emblica* potentiates indomethacin-induced gastric ulcer healing via e-nos-dependent pathway. Evidence-Based Complement Altern Med 2012;2012:487380.
[64] Kapoor MP, Suzuki K, Derek T, Ozeki M, Okubo T. Clinical evaluation of Emblica Officinalis Gatertn (Amla) in healthy human subjects: health benefits and safety results from a randomized, double-blind, crossover placebo-controlled study. Contemp Clin Trials Commun 2019;17:100499.
[65] Trivedi MK, Mondal SC, Gangwar M, Jana S. Effect of a novel ashwagandha-based herbomineral formulation on pro-inflammatory cytokines expression in mouse splenocyte cells: a potential immunomodulator. Phcog Mag 2017;13:S90.

[66] Mishra LC, Singh BB, Dagenais S. Scientific basis for the therapeutic use of *Withania somnifera* (ashwagandha): a review. Alternative Med Rev 2000;5:334–46.
[67] Uddin Q, Samiulla L, Singh VK, Jamil SS. Phytochemical and pharmacological profile of *Withania somnifera* dunal: a review. J Appl Pharmaceut Sci 2012;2:170–5.
[68] Sikandan A, Shinomiya T, Nagahara Y. Ashwagandha root extract exerts anti-inflammatory effects in HaCaT cells by inhibiting the MAPK/NF-κB pathways and by regulating cytokines. Int J Mol Med 2018;42:425–34.
[69] Muralikrishnan G, Dinda AK, Shakeel F. Immunomodulatory effects of *Withania somnifera* on azoxymethane induced experimental colon cancer in mice. Immunol Invest 2010;39:388–98.
[70] Shyni GL, Sindhu G, Helen A. Downregulation of inflammatory mediators and pro-inflammatory cytokines by alkaloids of *jeevaneeya rasayana* in adjuvant-induced arthritis. Immunol Invest 2015;44:70–87.
[71] Ku SK, Bae JS. Antiplatelet, anticoagulant, and profibrinolytic activities of withaferin A. Vasc Pharmacol 2014;60:120–6.
[72] Muthulakshmi M, Subramani PA, Michael RD. Immunostimulatory effect of the aqueous leaf extract of Phyllanthus niruri on the specific and nonspecific immune responses of Oreochromis mossambicus Peters. Iran J Vet Res 2016;17:200.
[73] Du G, Xiao M, Yu S, Wang M, Xie Y, Sang S. Phyllanthus urinaria: a potential phytopharmacological source of natural medicine 2018;11:6509–20.
[74] Shen ZQ, Chen P, Duan L, Dong ZJ, Chen ZH, Liu JK. Effects of fraction from Phyllanthus urinaria on thrombosis and coagulation system in animals 2004;2:15339469. Zhong Xi Yi Jie He Xue Bao.
[75] Harikrishnan H, Jantan I, Haque MA, Kumolosasi E. Phyllanthin from Phyllanthus amarus inhibits LPS-induced proinflammatory responses in U937 macrophages via downregulation of NF-κB/MAPK/PI3K-Akt signaling pathways. Phyther Res 2018;32:2510-2519.
[76] Soni P, Siddiqui AA, Dwivedi J, Soni V. Pharmacological properties of Datura stramonium L. as a potential medicinal tree: an overview. Asian Pac J Trop Biomed 2012;2:1002–8.
[77] Arora P, Ansari SH, Anjum V, Mathur R, Ahmad S. Investigation of anti-asthmatic potential of Kanakasava in ovalbumin-induced bronchial asthma and airway inflammation in rats. J Ethnopharmacol 2017;197:242–9.
[78] Fatoba TA, Adeloye AA, Soladoye AO. Effect of Datura stramonium seed extracts on haematological parameters of West African Dwarf (WAD) bucks. Eur J Exp Biol 2013;3:1–6.
[79] Anantha Krishna TH. Anti-thrombotic secondary metabolites from endophytic fungi of Datura metel and Cassia fistula. 2017 [Doctoral dessertation)].
[80] Nassiri-Asl M, Hosseinzadeh H. Review of the pharmacological effects of Vitis vinifera (grape) and its bioactive constituents: an update. Phyther Res 2016;30:1392–403.
[81] Zhang Y, Shi H, Wang W, Ke Z, Xu P, Zhong Z, et al. Antithrombotic effect of grape seed proanthocyanidins extract in a rat model of deep vein thrombosis. J Vasc Surg 2011;53:743–53.
[82] Dresch RR, Dresch MK, Guerreiro AF, Biegelmeyer R, Holzschuh MH, Rambo DF, et al. Phenolic compounds from the leaves of vitis labrusca and Vitis vinifera L. As a source of waste byproducts: development and validation of LC method and antichemotactic activity. Food Anal Methods 2014;7:527–39.
[83] Choudhary N, Siddiqui MB, Azmat S, Khatoon S. Tinospora cordifolia: ethnobotany, phytopharmacology and phytochemistry aspects. IJPSR 2013;4:891–9.
[84] Sannegowda KM, Venkatesha SH, Moudgil KD. Tinospora cordifolia inhibits autoimmune arthritis by regulating key immune mediators of inflammation and bone damage. Int J Immunopathol Pharmacol 2015;28:521–31.
[85] Lugun O, Bhoi S, Kujur P, Kumar D, Surin WR. Evaluation of antithrombotic activities of Solanum xanthocarpum and Tinospora cordifolia. Pharmacogn Res 2018;10:98–103. https://doi.org/10.4103/pr.pr_80_17.
[86] Mittal J, Sharma MM, Batra A. Tinospora cordifolia: a multipurpose medicinal plant-A review. J Med Plants Stud Year J Med Plants Stud 2014;2:32–47.
[87] Badar VA, Thawani VR, Wakode PT, Shrivastava MP, Gharpure KJ, Hingorani LL, et al. Efficacy of *Tinospora cordifolia* in allergic rhinitis. J Ethnopharmacol 2005;96:445–9.
[88] Patgiri B, Umretia B, Vaishnav P, Prajapati P, Shukla V, Ravishankar B. Anti-inflammatory activity of Guduchi Ghana (aqueous extract of Tinospora cordifolia miers.). AYU (An Int Q J Res Ayurveda) 2014;35:108.
[89] Ashraf K, Sultan S. A comprehensive review on Curcuma longa Linn.: phytochemical, pharmacological, and molecular study. Int J Green Pharm 2017;11:S671–85.
[90] Larmonier CB, Midura-Kiela MT, Ramalingam R, Laubitz D, Janikashvili N, Larmonier N, et al. Modulation of neutrophil motility by curcumin: implications for inflammatory bowel disease. Inflamm Bowel Dis 2011;17:503–15.
[91] Avasarala S, Zhang F, Liu G, Wang R, London SD, London L. Curcumin modulates the inflammatory response and inhibits subsequent fibrosis in a mouse model of viral-induced acute respiratory distress syndrome. PloS One 2013;8:e0134982.
[92] Srivastava R. Inhibition of neutrophil response by curcumin. Agents Actions 1989;28:298–303.
[93] Sirisidthi K, Kosai P, Jiraungkoorskul K, Jiraungkoorskul W. Antithrombotic activity of turmeric (Curcuma longa): a review. Indian J Agric Res 2016;50:101–6.
[94] Abu Bin Nyeem M, Abdul Mannan M, Nuruzzaman M, Kamrujjaman K, Kumar Das S. Indigenous king of bitter (Andrographis paniculata): a review. J Med Plants Stud 2017;5:318–24.
[95] Shen Y-C, Chen C-F, Chiou W-F. Andrographolide prevents oxygen radical production by human neutrophils: possible mechanism(s) involved in its anti-inflammatory effect. Br J Pharmacol 2002;135:399–406.
[96] Zhao HY, Fang WY. Antithrombotic effects of Andrographis paniculata nees in preventing myocardial infarction. Chin Med J 1991;104:770–5.
[97] Tekuri SK, Pasupuleti SK, Konidala KK, Amuru SR, Bassaiahgari P, Pabbaraju N. Phytochemical and pharmacological activities of Solanum surattense Burm. f.-A review. J Appl Pharmaceut Sci 2019;9:126–36.
[98] Kavita Gulati, et al. Evaluation of anti-inflammatory and immunomodulatory effects of aqueous extract of Solanum xanthocarpum in experimental models of bronchial asthma. EC Pharmacology and Toxicology 2016:241–50.
[99] Sultana R, Khanam S, Devi K. Immunomodulatory effect of methanol extract of Solanum xanthocarpum fruits. Int J Pharma Sci Res 2011;2:93–7.
[100] Manek R, Sheth N, Chavda J, Vaghasiya J, Modi K, Patel D. Liquorice exaggerates protective action of Solanum xanthocarpum against cigarette smoke induced pulmonary inflammation. Planta Med 2014;80.
[101] Ahmad S, Ali M, Ansari SH, Ahmed F. Phytoconstituents from the galls of pistacia integerrima stewart. J Saudi Chem Soc 2010;14:409–12.
[102] Shirole RL, Shirole NL, Kshatriya AA, Kulkarni R, Saraf MN. Investigation into the mechanism of action of essential oil of Pistacia integerrima for its anti-asthmatic activity. J Ethnopharmacol 2014;153:541–51.
[103] Rana S, Shahzad M, Shabbir A. Pistacia integerrima ameliorates airway inflammation by attenuation of TNF-α, IL-4, and IL-5 expression levels, and pulmonary edema by elevation of AQP1 and AQP5 expression levels in mouse model of ovalbumin-induced allergic asthma. Phytomedicine 2016 Jul 15;23(8):838–45.
[104] Mikaili P, Maadirad S, Moloudizargari M, Aghajanshakeri S, Sarahroodi S. Therapeutic uses and pharmacological properties of garlic, shallot, and their biologically active compounds. Iran J Basic Med Sci 2013;16:1031–48.
[105] Hobauer R, Frass M, Gmeiner B, Kaye AD, Frost EA. Garlic extract (allium sativum) reduces migration of neutrophils through endothelial cell monolayers. Middle East J Anesthesiol 2000;15:649–58.
[106] Hsieh CC, Liu KF, Liu PC, Ho YT, Li WS, Peng WH, et al. Comparing the protection imparted by different fraction extracts of garlic (Allium sativum l.) against der p–induced allergic airway inflammation in mice. Int J Mol Sci 2019;20:4879.
[107] Block E, Bechand B, Gundala S, Vattekkatte A, Wang K, Mousa SS, et al. Fluorinated analog NMR s of organosulfur compounds from garlic (allium sativum): synthesis, chemistry and anti-angiogenesis and antithrombotic studies. Molecules 2017;22:1–20.
[108] El-Sabban F, Fahim MA, Radwan GMH, Zaghloul SS, Singh S. Garlic preserves patency and delays hyperthermia-induced thrombosis in pial microcirculation. Int J Hyperther 1996;12:513–25.
[109] Bui TT, Piao CH, Song CH, Shin HS, Shon DH, Chai OH. Piper nigrum extract ameliorated allergic inflammation through inhibiting Th2/Th17 responses and mast cells activation. Cell Immunol 2017;322:64–73.
[110] Stojanović-Radić Z, Pejčić M, Dimitrijević M, Aleksić A, Anil Kumar NV, Salehi B, et al. Piperine-A major principle of black pepper: a review of its bioactivity and studies. Appl Sci 2019;9:4270.
[111] Kumar S, Malhotra S, Prasad A, Eycken E, Bracke M, Stetler-Stevenson W, et al. Anti-inflammatory and antioxidant properties of piper species: a perspective from screening to molecular mechanisms. Curr Top Med Chem 2015;15:886–93.
[112] Majdalawieh AF, Carr RI. In vitro investigation of the potential immunomodulatory and anti-cancer activities of black pepper (Piper nigrum) and cardamom (Elettaria cardamomum). J Med Food 2010;13:371–81.
[113] Singh A, Navneet. Critical review on various ethonomedicinal and pharmacological aspects of piper longum linn. (long pepper or pippali). Int J Innov Pharm Sci Res 2018;6:48–60.
[114] Singh N, Kumar S, Singh P, Raj HG, Prasad AK, Parmar VS, et al. Piper longum Linn. Extract inhibits TNF-α-induced expression of cell adhesion molecules by inhibiting NF-κB activation and microsomal lipid peroxidation. Phytomedicine 2008;15:284–91.
[115] Bae GS, Kim MS, Jeong J, Lee HY, Park KC, Koo BS, et al. Piperine ameliorates the severity of cerulein-induced acute pancreatitis by inhibiting the activation of mitogen activated protein kinases. Biochem Biophys Res Commun 2011;410:382–8.
[116] Singh N, Nath R, Gupta ML, Kohli RP. An experimental evaluation of anti-asthmatic potentialitis of inula racemosa (puskar mul). Pharm Biol 1980;18:89–96.
[117] Ojha S, Bharti S, Sharma AK, Rani N, Bhatia J, et al. Effect of Inula racemosa root extract on cardiac function and oxidative stress against isoproterenol-induced myocardial infarction. Indian J Biochem Biophys 2011;48:22–8.
[118] Arumugam Ponnan. Evaluation of anti-inflammatory and analgesic effects of aqueous extract obtained from root powder of Inula racemosa Hook. f. J Med Plants Res 2012;6:2801–6.
[119] Kajaria D, Tripathi J, Tiwari SK, Pandey BL. In-vitro evaluation of immunomodulatory effect of polyherbal compound bharangyadi. J Drug Deliv Therapeut 2013;3:36–9.
[120] Mishra A, Thakur M, Alok S. Valuation of immunomodulatory activity of polysacchride fraction of inula racemosa, bombax ceiba and allium sativum. IJPSR 2016;7:3749–55.

[121] Arulmozhi S, Mazumder P, Ashok P, Narayanan LS. Pharmacological activities of Alstonia scholaris linn. (Apocynaceae)-A review. Phcog Rev 2007;1:163–70.
[122] Atmaram DA, Sudhakar BS, Premal MR. Effect of the aqueous extract of bark of Alstonia schlolaris Linn. on respiratory burst in Polymorphonuclear Neutrophils (PMNs). Int J Res Ayurveda Pharm 2012;3.
[123] Zhao YL, Cao J, Shang JH, Liu YP, Khan A, Wang HS, et al. Airways antiallergic effect and pharmacokinetics of alkaloids from Alstonia scholaris. Phytomedicine 2017;27:63–72.
[124] Hasan N, Ahmad N, Zohrameena S, Khalid M, Akhtar J. Asparagus racemosus: for medicinal uses & pharmacological actions. Int J Adv Res 2016;4:259–67.
[125] Shaha P, Bellankimath A. Pharmacological profile of Asparagus racemosus: a review. Int J Curr Microbiol Appl Sci 2017;6:1215–23.
[126] Alok S, Jain SK, Verma A, Kumar M, Mahor A, Sabharwal M. Plant profile, phytochemistry and pharmacology of Asparagus racemosus (Shatavari): a review. Asian Pacific J Trop Dis 2013;3:242–51.
[127] Rasool S, Maqbool M. An overview about Hedychium spicatum: a review. J Drug Deliv Therapeut 2019;9:476–80.
[128] Uttara J, Mishra SH. Preliminary evaluation of immunomodulatory and antistress activity of methanol extract of Hedychium spicatum. Pharmacologyonline 2009;1:1057–71.
[129] Ahui MLB, Champy P, Ramadan A, Pham Van L, Araujo L, Brou André K, et al. Ginger prevents Th2-mediated immune responses in a mouse model of airway inflammation. Int Immunopharm 2008;8:1626–32.
[130] Lee W, Ku SK, Kim MA, Bae JS. Anti-factor Xa activities of zingerone with anti-platelet aggregation activity. Food Chem Toxicol 2017;105:186–93.
[131] Imtiyaz S, Rahman K, Sultana A, Tariq M, Chaudhary SS. Zingiber officinale Rosc.: a traditional herb with medicinal properties. TANG 2013;3:e26.
[132] Khan AM, Shahzad M, Raza Asim MB, Imran M, Shabbir A. Zingiber officinale ameliorates allergic asthma via suppression of Th2-mediated immune response. Pharm Biol 2015;53:359–67.
[133] Yadav DK, Ghosh AK. A review of pharmacognostical, phytochemical and pharmacological effect of abeis webbiana lindl. Leaves 2015;4:736–40.
[134] Hemalatha R, Narendra Babu K, Karthik M, Ramesh R, Dinesh Kumar B, Uday Kumar P. Immunomodulatory activity and Th1/Th2 cytokine response of Ocimum sanctum in myelosuppressed swiss albino mice. Trends Med Res 2011;6:23–31.
[135] Pandey G. Pharmacological activities of ocimum sanctum (tulsi): a review. Int J Pharmaceut Sci Rev Res 2010;5.
[136] Archana R, Namasivayam A. Effect of Ocimum sanctum on noise induced changes in neutrophil functions. J Ethnopharmacol 2000;73:81–5.
[137] Goel A, Singh DK, Kumar S, Bhatia AK. Immunomodulating property of Ocimum sanctum by regulating the IL-2 production and its mRNA expression using rat's splenocytes. Asian Pac J Trop Med 2010;3:8–12.
[138] Goel A, Kumar S, Singh DK, Bhatia AK. Wound healing potential of ocimum sanctum linn. with induction of tumor necrosis-α. Indian J Exp Biol 2010;48:402–6.
[139] Khan IN, Habib MR, Rahman MM, Mannan A, Sarker MMI, Hawlader S. Thrombolytic potential of Ocimum sanctum L., Curcuma longa L., Azadirachta indica L. and Anacardium occidentale L. J Basic Clin Pharm 2011;2:125.
[140] Fahad M, Khan MM, Tahir M, Jameel MN, Ahmad MA, Khushtar M. Medicinal and pharmacological role of traditional Asian Food condiment. Cinnamomum zeylanicum Blume 2018;6:22–30.
[141] Niphade SR, Asad M, Chandrakala GK, Toppo E, Deshmukh P. Immunomodulatory activity of Cinnamomum zeylanicum bark. Pharm Biol 2009;47:1168–73.
[142] Balekar N, Bodhankar S, Mohan V, Thakurdesai PA. Modulatory activity of a polyphenolic fraction of Cinnamomum zeylanicum L. bark on multiple arms of immunity in normal and immunocompromised mice. J Appl Pharmaceut Sci 2014;7:114–22.
[143] Kumar Singh Scholar S, Ram Patel J, Dangi A, Bachle D, Kumar Kataria R, Santosh Kumar Singh Scholar C, et al. A complete over review on Adhatoda vasica a traditional medicinal plants. J Med Plants Stud 2017;5:175–80.
[144] Gupta A, Prajapati PK, Choudhary AK. A comparative study of the effect of vasa avaleha prepared with vasa swarasa and vasa kwatha in tamaka Shwasa. Ancient Sci Life 2009;3:23–8.
[145] Zanasi A, Mazzolini M, Kantar A. A reappraisal of the mucoactive activity and clinical efficacy of bromhexine. Multidiscip Respir Med 2017;12:1.
[146] Vinothapooshan G, Sundar K. Immunomodulatory activity of various extracts of Adhatoda vasica Linn. in experimental rats. African J Pharm Pharmacol 2011;3:306–10.
[147] Mahmud S, Akhter S, Rahman MA, Aklima J, Akhter S, Merry SR, et al. Antithrombotic effects of five organic extracts of bangladeshi plants in vitro and mechanisms in in silico models. Evidence-Based Complement Altern Med 2015;2015:782742.
[148] Kim SH, Hong JH, Yang WK, Geum JH, Kim HR, Choi SY, et al. Herbal combinational medication of *glycyrrhiza glabra* and *agastache rugosa* containing glycyrrhizic acid, tilianin inhibits neutrophilic lung inflammation by affecting cxcl2, interleukin17/stat3 signal pathways in a murine model of copd. Nutrients 2020;12:926.
[149] Mendes-Silva W, Assafim M, Ruta B, Monteiro RQ, Guimarães JA, Zingali RB. Antithrombotic effect of Glycyrrhizin, a plant-derived thrombin inhibitor. Thromb Res 2003;112:93–8.
[150] Sharma V, Katiyar A, Agrawal RC. Glycyrrhiza glabra: chemistry and pharmacological activity. Sweetners. Springer International Publishing AG; 2018. p. 87–100 [Reference series in phytochemistry].
[151] Li C, Eom T, Jeong Y. Glycyrrhiza glabra L. extract inhibits LPS-induced inflammation in RAW macrophages. J Nutr Sci Vitaminol 2015;61:375–81.
[152] Wang X rong, guang Hao H, Chu L. Glycyrrhizin inhibits LPS-induced inflammatory mediator production in endometrial epithelial cells. Microb Pathog 2017;109:110–3.
[153] Liu Z, Zhong JY, Gao EN, Yang H. Effects of glycyrrhizin acid and licorice flavonoids on LPS-induced cytokines expression in macrophage. Zhongguo Zhongyao Zazhi 2014;19:3841–5.
[154] Badmaev V, Nowakowski M. Protection of epithelial cells against influenza A virus by a plant derived biological response modifier Ledretan-96. Phyther Res 2000;14:245–9.
[155] Kurokawa M, Nagasaka K, Hirabayashi T, Uyama S ichi, Sato H, Kageyama T, et al. Efficacy of traditional herbal medicines in combination with acyclovir against herpes simplex virus type 1 infection in vitro and in vivo. Antivir Res 1995;27:19–37.
[156] Sharma V, Katiyar A, Agrawal RC. Glycyrrhiza glabra: chemistry and pharmacological activity. Sweeteners. Nature Publishing Group; 2018. p. 87–100.
[157] Bagalkotkar G, Sagineedu SR, Saad MS, Stanslas J. Phytochemicals from Phyllanthus niruri Linn. and their pharmacological properties: a review. J Pharm Pharmacol 2006;58:1559–70.
[158] Hsieh CC, Peng WH, Tseng HH, Liang SY, Chen LJ, Tsai JC. The protective role of garlic on allergen-induced airway inflammation in mice. Am J Chin Med 2019;47:1099–112.
[159] Barnes PJ. Cytokine modulators as novel therapies for airway disease. European Respiratory Society Eur Respir J Suppl 2001;18:67s–77s. 34.
[160] Qabaha K, Abu-Lafi S, Al-Rimawi F. Anti - inflammatory activities of ethanolic extracts of curcuma longa (turmeric) and cinnamon (Cinnamomum verum). J Food Nutr Res 2017;5:668–73.
[161] Salehi B, Zakaria ZA, Gyawali R, Ibrahim SA, Rajkovic J, Shinwari ZK, et al. Piper species: a comprehensive review on their phytochemistry, biological activities and applications. Molecules 2019;24:1364.
[162] Yadav V, Krishnan A, Vohora D. A systematic review on Piper longum L.: bridging traditional knowledge and pharmacological evidence for future translational research. J Ethnopharmacol 2020;247:112255.
[163] Ahmad F, Ali M, Alam P. New phytoconstituents from the stem bark of *Tinospora cordifolia* Miers. Nat Prod Res 2010;24:926–34.
[164] Liao PC, Lai MH, Hsu KP, Kuo YH, Chen J, Tsai MC, et al. Identification of β-Sitosterol as in vitro anti-inflammatory constituent in *Moringa oleifera*. J Agric Food Chem 2018;41:10748–59.
[165] Zhang H, Shan Y, Wu Y, Xu C, Yu X, Zhao J, et al. Berberine suppresses LPS-induced inflammation through modulating Sirt1/NF-κB signaling pathway in RAW264.7 cells. Int Immunopharm 2017;52:93–100.
[166] Wang W, Zha G, Zou J jing, Wang X, nian Li C, Wu X jun. Berberine attenuates cigarette smoke extract-induced airway inflammation in mice: involvement of TGF-β1/Smads signaling pathway. Curr Med Sci 2019;39:748–53.
[167] Sharma U, Bala M, Kumar N, Singh B, Munshi RK, Bhalerao S. Immunomodulatory active compounds from *Tinospora cordifolia*. J Ethnopharmacol 2012;141:918–26.
[168] Kim MG, Kim SM, Min JH, Kwon OK, Park MH, Park JW, et al. Anti-inflammatory effects of linalool on ovalbumin-induced pulmonary inflammation. Int Immunopharm 2019;74.
[169] Brito LF, Oliveira HBM, das Neves Selis N, e Souza CLS, Júnior MNS, de Souza EP, et al. Anti-inflammatory activity of β-caryophyllene combined with docosahexaenoic acid in a model of sepsis induced by *Staphylococcus aureus* in mice. J Sci Food Agric 2019;99:5870–80.
[170] Siqueira HDAS, Neto BS, Sousa DP, Gomes BS, da Silva FV, Cunha FVM, et al. α-Phellandrene, a cyclic monoterpene, attenuates inflammatory response through neutrophil migration inhibition and mast cell degranulation. Life Sci 2016;160:27–33.
[171] Chen L, Zhao L, Zhang C, Lan Z. Protective effect of p-cymene on lipopolysaccharide-induced acute lung injury in mice. Inflammation 2014;37:358–64.
[172] Clapp PW, Pawlak EA, Lackey JT, Keating JE, Reeber SL, Glish GL, et al. Flavored e-cigarette liquids and cinnamaldehyde impair respiratory innate immune cell function. Am J Physiol Lung Cell Mol Physiol 2017;313:278–92.
[173] Uteshev DB, Kostriukov EB, Karabinenko AA, Kovaleva VL, Makarova OV, Storozhakov GI. The anti-inflammatory activity of intal and beta-carotene in a model of experimental granulomatous lung inflammation. Patol Fiziol Eksp Ter 2000:19–22.
[174] Kumar S, Saxena K, Uday I, Singh N, Saxena R, Singh UN. Anti-inflammatory action of ginger: a critical review in anemia of inflammation and its future aspects. Int J Herb Med 2013;1:16–20.
[175] Ali RA, Knight JS. Natural gingerols inhibit neutrophil extracellular trap release elicited by lupus autoantibodies [abstract]. Arthritis Rheum 2018:70.
[176] Nogueira De Melo GA, Grespan R, Fonseca JP, Farinha TO, Da Silva EL, Romero AL, et al. Inhibitory effects of ginger (*Zingiber officinale* Roscoe) essential oil on leukocyte migration in vivo and in vitro. J Nat Med 2011;65:241–6.
[177] Xie X, Sun S, Zhong W, Soromou LW, Zhou X, Wei M, et al. Zingerone attenuates lipopolysaccharide-induced acute lung injury in mice. Int Immunopharm 2014;19:103–9.

[178] Sharma U, Kumar N, Singh B, Munshi RK, Bhalerao S. Immunomodulatory active steroidal saponins from Asparagus racemosus. Med Chem Res 2013;22:573–9.
[179] Gao Z, Xu H, Chen X, Chen H. Antioxidant status and mineral contents in tissues of rutin and baicalin fed rats. Life Sci 2003;73:1599–607.
[180] Saija A, Tomaino A, Trombetta D, Pellegrino ML, Tita B, Messina C, et al. "In vitro" antioxidant and photoprotective properties and interaction with model membranes of three new quercetin esters. Eur J Pharm Biopharm 2003;55. 357-0.
[181] Jablonska E, Garley M, Surazynski A, Grubczak K, Iwaniuk A, Borys J, et al. Neutrophil extracellular traps (NETs) formation induced by TGF-β in oral lichen planus – possible implications for the development of oral cancer. Immunobiology 2020;225.
[182] Pincemail J, Deby C, Thirion A, de Bruyn-Dister M, Goutier R. Human myeloperoxidase activity is inhibited in vitro by quercetin. Comparison with three related compounds. Experientia 1988;44:450–3.
[183] Joshi B, Prasad Sah G, Bahadur Basnet B, Raj Bhatt M, Sharma D, Subedi K, et al. Phytochemical extraction and antimicrobial properties of different medicinal plants: *Ocimum sanctum* (Tulsi), *Eugenia caryophyllata* (Clove), *Achyranthes bidentata* (Datiwan) and *Azadirachta indica* (Neem). J Microbiol Antimicrob 2011;3:1–7.
[184] Samson J, Sheeladevi R, Ravindran R. Oxidative stress in brain and antioxidant activity of Ocimum sanctum in noise exposure. Neurotoxicology 2007;28:679–85.
[185] Kelm MA, Nair MG, Strasburg GM, DeWitt DL. Antioxidant and cyclooxygenase inhibitory phenolic compounds from *Ocimum sanctum* Linn. Phytomedicine 2000;7:7–13.
[186] Singh D, Chaudhuri PK. A review on phytochemical and pharmacological properties of Holy basil (*Ocimum sanctum* L.). Ind Crop Prod 2018;118:367–82.
[187] Verma H, Nagar S, Mahapatra B, Shukla Anil, Paul J. Evaluation of an emerging medicinal crop Kalmegh [*Andrographis paniculata* (Burm. F.) Wall. Ex. Nees] for commercial cultivation and pharmaceutical & industrial uses: a review. J Pharmacogn Phytochem 2019;8:835–48.
[188] Reddy VLN, Reddy SM, Ravikanth V, Krishnaiah P, Goud TV, Rao TP, et al. A new bis-andrographolide ether from *Andrographis paniculata* nees and evaluation of anti-HIV activity. Nat Prod Res 2005;19:223–30.
[189] Puri A, Saxena R, Saxena RP, Saxena KC, Srivastava V, Tandon JS. Immunostimulant agents from *Andrographis paniculata*. J Nat Prod 1993;56:995–9.
[190] Mohammed BM, Fisher BJ, Kraskauskas D, Farkas D, Brophy DF, Fowler AA, et al. Vitamin C: a novel regulator of neutrophil extracellular trap formation. Nutrients 2013;8:3131–50.
[191] Moon P-D, Lee B-H, Jeong H-J, An H-J, Park S-J, Kim H-R, et al. Use of scopoletin to inhibit the production of inflammatory cytokines through inhibition of the IkappaB/NF-kappaB signal cascade in the human mast cell line HMC-1. Eur J Pharmacol 2007;555:218–25.
[192] Kuo PL, Huang YT, Chang CH, Chang JK. Fraxetin inhibits the induction of anti-Fas IgM, tumor necrosis factor-α and interleukin-1β-mediated apoptosis by Fas pathway inhibition in human osteoblastic cell line MG-63. Int Immunopharm 2006;6:1167–75.
[193] Song L, Chu R, Cao Z. The effects of scopolamine on the survival time and microcirculation of septic shock rats. Eur J Pharmaceut Sci 2020:141.
[194] Wu XJ, Liu HM, Song XM, Zhao B, Leng Y, Wang EY, et al. Penehyclidine hydrochloride inhibits TLR4 signaling and inflammation, and attenuates blunt chest trauma and hemorrhagic shock-induced acute lung injury in rats. Mol Med Rep 2018;17:6327–36.
[195] Panahi Y, Ghanei M, Bashiri S, Hajihashemi A, Sahebkar A. Short-term curcuminoid supplementation for chronic pulmonary complications due to sulfur mustard intoxication: positive results of a randomized double-blind placebo-controlled trial. Drug Res 2014;65:567–75.
[196] Liu Z, Ying Y. The inhibitory effect of curcumin on virus-induced cytokine storm and its potential use in the associated severe pneumonia. Front Cell Dev Biol 2020;2020:479.
[197] Sordillo PP, Helson L. Curcumin suppression of cytokine release and cytokine storm. A potential therapy for patients with Ebola and other severe viral infections. In Vivo 2015;29:1–4.
[198] Park SY, Jin ML, Kim YH, Kim Y, Lee SJ. Anti-inflammatory effects of aromatic-turmerone through blocking of NF-κB, JNK, and p38 MAPK signaling pathways in amyloid β-stimulated microglia. Int Immunopharm 2012;14. 99-06.
[199] Reynoso-Moreno I, Najar-Guerrero I, Escareno N, Flores-Soto ME, Gertsch J, Viveros-Paredes JM. An endocannabinoid uptake inhibitor from black pepper exerts pronounced anti-inflammatory effects in mice. J Agric Food Chem 2017;65:9435–42.
[200] Aswar U, Shintre S, Chepurwar S, Aswar M. Antiallergic effect of piperine on ovalbumin-induced allergic rhinitis in mice. Pharm Biol 2015;53:1358–66.
[201] Wang-Sheng C, Jie A, Jian-Jun L, Lan H, Zeng-Bao X, Chang-Qing L. Piperine attenuates lipopolysaccharide (LPS)-induced inflammatory responses in BV2 microglia. Int Immunopharm 2017;42:44–8.
[202] Herman S, Kny A, Schorn C, Pfatschbacher J, Niederreiter B, Herrmann M, et al. Cell death and cytokine production induced by autoimmunogenic hydrocarbon oils. Autoimmunity 2012;8:602–11.
[203] Lu C, Zhang B, Xu T, Zhang W, Bai B, Xiao Z, et al. Piperlongumine reduces ovalbumin-induced asthma and airway inflammation by regulating nuclear factor-κB activation. Int J Mol Med 2019;44:1855–65.
[204] de Christo Scherer MM, Marques FM, Figueira MM, Peisino MCO, Schmitt EFP, Kondratyuk TP, et al. Wound healing activity of terpinolene and α-phellandrene by attenuating inflammation and oxidative stress in vitro. J Tissue Viability 2019;28:94–9.
[205] Kumar A, Agarwal K, Singh M, Saxena A, Yadav P, Maurya AK, et al. Essential oil from waste leaves of *Curcuma longa* L. alleviates skin inflammation. Inflammopharmacology 2018;5:1245–55.
[206] Yoon WJ, Moon JY, Song G, Lee YK, Han MS, Lee JS, et al. Artemisia fukudo essential oil attenuates LPS-induced inflammation by suppressing NF-κB and MAPK activation in RAW 264.7 macrophages. Food Chem Toxicol 2010;48:1222–9.
[207] Zhang H, Shang C, Tian Z, Amin HK, Kassab RB, Abdel Moneim AE, et al. Diallyl disulfide suppresses inflammatory and oxidative machineries following carrageenan injection-induced paw edema in mice. Mediat Inflamm 2020;2020:8508906.
[208] Lee HH, Han MH, Hwang HJ, Kim GY, Moon SK, Hyun JW, et al. Diallyl trisulfide exerts anti-inflammatory effects in lipopolysaccharide-stimulated RAW 264.7 macrophages by suppressing the Toll-like receptor 4/nuclear factor-κ B pathway. Int J Mol Med 2015;35:487–95.
[209] Wang Y-L, Guo X-Y, He W, Chen R-J, Zhuang R. Effects of alliin on LPS-induced acute lung injury by activating PPARγ. Microb Pathog 2017;110:375–9.
[210] Thomaz L, Apitz-Castro R, Marques AF, Travassos LR, Taborda CP. Experimental paracoccidioidomycosis: alternative therapy with ajoene, compound from *Allium sativum*, associated with sulfamethoxazole/trimethoprim. Med Mycol 2008;46:113–8.
[211] Romano EL, Montaño RF, Brito B, Apitz R, Alonso J, Romano M, et al. Effects of Ajoene on lymphocyte and macrophage membrane-dependent functions. Immunopharmacol Immunotoxicol 1997;19:15–36.
[212] Shin JH, Ryu JH, Kang MJ, Hwang CR, Han J, Kang D. Short-term heating reduces the anti-inflammatory effects of fresh raw garlic extracts on the LPS-induced production of NO and pro-inflammatory cytokines by down-regulating allicin activity in RAW 264.7 macrophages. Food Chem Toxicol 2013;58:545–51.
[213] Shen N, Cheng A, Qiu M, Zang G. Allicin improves lung injury induced by sepsis via regulation of the toll-like receptor 4 (TLR4)/myeloid differentiation primary response 88 (MYD88)/nuclear factor kappa b (NF-κB) pathway. Med Sci Mon Int Med J Exp Clin Res 2019;25:2567.
[214] Jiang T, Zhang L, Ding M, Li M. Protective effect of vasicine against myocardial infarction in rats via modulation of oxidative stress, inflammation, and the PI3K/akt pathway. Drug Des Dev Ther 2019;13:3773–84.
[215] Vugic L, Colson N, Nikbakht E, Gaiz A, Holland OJ, Kundur AR, et al. Anthocyanin supplementation inhibits secretion of pro-inflammatory cytokines in overweight and obese individuals. J Funct Foods 2020;64:103596.
[216] Yu JY, Ha JY, Kim KM, Jung YS, Jung JC, Oh S. Anti-inflammatory activities of licorice extract and its active compounds, glycyrrhizic acid, liquiritin and liquiritigenin, in BV2 cells and mice liver. Molecules 2015;20:13041–54.
[217] Checker R, Sandur SK, Sharma D, Patwardhan RS, Jayakumar S, Kohli V, et al. Potent anti-inflammatory activity of ursolic acid, a triterpenoid antioxidant, is mediated through suppression of NF-κB, AP-1 and NF-AT. PloS One 2012;7:e31318.
[218] Ahmad SF, Zoheir KMA, Abdel-Hamied HE, Attia SM, Bakheet SA, Ashour AE, et al. Grape seed proanthocyanidin extract protects against carrageenan-induced lung inflammation in mice through reduction of pro-inflammatory markers and chemokine expressions. Inflammation 2014;37:500–11.
[219] Terra X, Montagut G, Bustos M, Llopiz N, Ardèvol A, Bladé C, et al. Grape-seed procyanidins prevent low-grade inflammation by modulating cytokine expression in rats fed a high-fat diet. J Nutr Biochem 2009;20:210–8.
[220] Bak MJ, Truong VL, Kang HS, Jun M, Jeong WS. Anti-inflammatory effect of procyanidins from wild grape (vitis amurensis) seeds in LPS-induced RAW 264.7 cells. Oxid Med Cell Longev 2013;2013.
[221] Bhattacharya A, Ghosal S, Bhattacharya SK. Anti-oxidant effect of Withania somnifera glycowithanolides in chronic footshock stress-induced perturbations of oxidative free radical scavenging enzymes and lipid peroxidation in rat frontal cortex and striatum. J Ethnopharmacol 2001;74:1–6.
[222] Rasool M, Chandal S, Sabina EP. Inhibition of monosodium urate crystal-induced inflammation by withaferin A. J Pharm Pharmaceut Sci 2008;11:46–55.
[223] Chen BW, Lin YC, Sheu JH. Structures and bioactivities of withanolides from the leaves of Solanum capsicoides. Planta Med 2015;81.
[224] Cheng Y, Liu Y, Tan J, Sun Y, Guan W, Jiang P, et al. Integrated serum metabolomics and network pharmacology approach to reveal the potential mechanisms of withanolides from the leaves of Datura metel L. on psoriasis. J Pharmaceut Biomed Anal 2020;186:113277.
[225] Bano N, Ahmed A, Tanveer M, Khan GM, Ansari MT. Pharmacological evaluation of Ocimum sanctum. J Bioequivalence Bioavailab 2017;9:387–492.
[226] Yuan K, Zhu Q, Lu Q, Jiang H, Zhu M, Li X, et al. Quercetin alleviates rheumatoid arthritis by inhibiting neutrophil inflammatory activities. J Nutr Biochem 2020;84:108454.
[227] Chuammitri P, Amphaiphan C, Nojit P. In vitro modulatory effects of quercetin on bovine neutrophil effector functions. The Thai Journal of Veterinary Medicine 2015;45:63–72.
[228] Hidalgo MA, Hancke JL, Bertoglio JC, Burgos RA. Andrographolide a new potential drug for the long-term treatment of rheumatoid arthritis disease. Hampshire, UK: InTech; 2013. p. 247–70.

[229] Li X, Yuan K, Zhu Q, Lu Q, Jiang H, Zhu M, et al. Andrographolide ameliorates rheumatoid arthritis by regulating the apoptosis–NETosis balance of neutrophils. Int J Mol Sci 2019;20:5035.
[230] Kanashiro A, Souza JG, Kabeya LM, Azzolini AECS, Lucisano-Valim YM. Elastase release by stimulated neutrophils inhibited by flavonoids: importance of the catechol group. Zeitschrift Fur Naturforsch - Sect C J Biosci 2007;62:357–61.
[231] Zeng J, Xu H, Fan P zhi, Xie J, He J, Yu J, et al. Kaempferol blocks neutrophil extracellular traps formation and reduces tumour metastasis by inhibiting ROS-PAD4 pathway. J Cell Mol Med 2020;24:7590–9.
[232] Lee NYS, Khoo WKS, Adnan MA, Mahalingam TP, Fernandez AR, Jeevaratnam K. The pharmacological potential of Phyllanthus niruri. J Pharm Pharmacol 2016;68:953-69.
[233] Pei H, Xue L, Tang M, Tang H, Kuang S, Wang L, et al. Alkaloids from black pepper (piper nigrum L.) exhibit anti-inflammatory activity in murine macrophages by inhibiting activation of NF-κB pathway. J Agric Food Chem 2020;68:2406–17.
[234] Almatroodi SA, Alrumaihi F, Alsahli MA, Alhommrani MF, Khan A, Rahmani AH. Curcumin, an active constituent of turmeric spice: implication in the prevention of lung injury induced by benzo(a) pyrene (BAP) in rats. Molecules 2020;25:724.
[235] Han S, Xu J, Guo X, Huang M. Curcumin ameliorates severe influenza pneumonia via attenuating lung injury and regulating macrophage cytokines production. Clin Exp Pharmacol Physiol 2018;45:84–93.
[236] Yang XX, Li CM, Huang CZ. Curcumin modified silver nanoparticles for highly efficient inhibition of respiratory syncytial virus infection. Nanoscale 2016;8:3040–8.
[237] Lorne E, Zmijewski JW, Zhao X, Liu G, Tsuruta Y, Park Y-J, et al. Role of extracellular superoxide in neutrophil activation: interactions between xanthine oxidase and TLR4 induce proinflammatory cytokine production. Am J Physiol Physiol 2008;294:C985–93.
[238] Li H, Pan P, Su X, Liu S, Zhang L, Wu D, et al. Neutrophil extracellular traps are pathogenic in ventilator-induced lung injury and partially dependent on TLR4. BioMed Res Int 2017;2017:8272504.
[239] Choudhury A, Mukherjee S. In silico studies on the comparative characterization of the interactions of SARS-CoV-2 spike glycoprotein with ACE-2 receptor homologs and human TLRs. J Med Virol 2020;92:2105–13.
[240] Schink A, Naumoska K, Kitanovski Z, Kampf CJ, Fröhlich-Nowoisky J, Thines E, et al. Anti-inflammatory effects of cinnamon extract and identification of active compounds influencing the TLR2 and TLR4 signaling pathways. Food Funct 2018;9:5950–64.
[241] Bhaskar S, Shalini V, Helen A. Quercetin regulates oxidized LDL induced inflammatory changes in human PBMCs by modulating the TLR-NF-κB signaling pathway. Immunobiology 2011;216:367–73.
[242] Carmona-Rivera C, Zhao W, Yalavarthi S, Kaplan MJ. Neutrophil extracellular traps induce endothelial dysfunction in systemic lupus erythematosus through the activation of matrix metalloproteinase-2. Ann Rheum Dis 2015;74:1417–24.
[243] Kanbarkar N, Mishra S. Matrix metalloproteinase inhibitors identified from Camellia sinensis for COVID - 19 prophylaxis : an in silico approach. Adv Tradit Med 2020:1–16.
[244] Branitzki-Heinemann K, Möllerherm H, Völlger L, Husein DM, de Buhr N, Blodkamp S, et al. Formation of neutrophil extracellular traps under low oxygen level. Front Immunol 2016;7:25.
[245] Ouyang S, Yao YH, Zhang ZM, Liu JS, Xiang H. Curcumin inhibits hypoxia inducible factor-1α-induced inflammation and apoptosis in macrophages through an ERK dependent pathway. Eur Rev Med Pharmacol Sci 2019;23:1816–25.
[246] Cuomo F, Coppola A, Botti C, Maione C, Forte A, Scisciola L, et al. Pro-inflammatory cytokines activate hypoxia-inducible factor 3α via epigenetic changes in mesenchymal stromal/stem cells. Sci Rep 2018;8:1–12.
[247] Egners A, Erdem M, Cramer T. The response of macrophages and neutrophils to hypoxia in the context of cancer and other inflammatory diseases. Mediat Inflamm 2016;2016:2053646.
[248] Stakos DA, Kambas K, Konstantinidis T, Mitroulis I, Apostolidou E, Arelaki S, et al. Expression of functional tissue factor by neutrophil extracellular traps in culprit artery of acute myocardial infarction. Eur Heart J 2015;36:1405–14.
[249] Skendros P, Mitsios A, Chrysanthopoulou A, Mastellos DC, Metallidis S, Rafailidis P, et al. Complement and tissue factor-enriched neutrophil extracellular traps are key drivers in COVID-19 immunothrombosis. J Clin Invest 2020;130:6151–7.
[250] Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Transl Res 2020;220:1.
[251] Ruhnau J, Schulze J, Dressel A, Vogelgesang A. Thrombosis, neuroinflammation, and poststroke infection: the multifaceted role of neutrophils in stroke. J Immunol Res 2017;2017:5140679.
[252] Fuchs TA, Brill A, Duerschmied D, Schatzberg D, Monestier M, Myers DD, et al. Extracellular DNA traps promote thrombosis. Proc Natl Acad Sci U S A 2010;107:15880–5.
[253] De Meyer SF, Suidan GL, Fuchs TA, Monestier M, Wagner DD. Extracellular chromatin is an important mediator of ischemic stroke in mice. Arterioscler Thromb Vasc Biol 2012;32:1884–91.
[254] Haselmayer P, Grosse-Hovest L, Von Landenberg P, Schild H, Radsak MP. TREM-1 ligand expression on platelets enhances neutrophil activation. Blood 2007;110:1029–35.
[255] Wohner N, Kovács A, MacHovich R, Kolev K. Modulation of the von Willebrand factor-dependent platelet adhesion through alternative proteolytic pathways. Thromb Res 2012;129:e41.