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Some Medicinal Plants with Ameliorative Potential on COVID-19 Cytokine Storm: A Review

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Abstract

COVID-19 is a global pandemic that has claimed over 6,000,000 deaths since its appearance in late 2019. It is caused by the virus SARS-CoV2. In severe COVID-19 patients, the transition to ARDS is primarily due to cytokine storm, which is characterised by excessive inflammatory response and elevated levels of ferritin and pro-inflammatory cytokines in the serum, infiltration of neutrophils and monocytes into the lung; and reduced viral inhibiting cytokines, all of which contribute to the severity of the disease leading to death. The focus of this review is on the collation of medicinal plants with strong anti-inflammatory activities, which could be used alone or synergistically for enhanced therapeutic effect to cushion cytokine storm damaging effects. The plants collated evidently show by in vitro and in vivo analysis strong anti-inflammatory effects via suppression of Interleukin-8, Interleukin-6, Interleukin-1α, Interleukin-1β, Tumor Necrosis Factor-α, Interferon-γ, monocyte chemo-attractant protein-1, and nuclear factor kappa B (NF-κB) expression, in addition to inhibiting cyclooxygenase I and II (COX I and II), and inducible nitric oxide synthase (iNOS) activity. The medicinal plants collated in this review could be used alone or synergistically in the future in clinics for enhanced therapeutic effects to cushion cytokine storm damaging effects. Isolation of the active principle and studies of the specific mechanism of action of the plants could be the objectives of future research.

Keywords: Medicinal Plants, Covid-19, Cytokine Storm

1. Introduction

Coronavirus Disease 2019 (COVID-19) is a respiratory disease implicated in having pneumonia-like symptoms characterised by dry cough, fever, sneezing, and fatigue. The disease was first reported in December, 2019 around Wuhan Province in the Hubei region of China [1]. The disease is highly contagious and spreads at an exponential rate within a very short period of time. It has crossed boundaries, affecting almost all nations and was pronounced a global pandemic by the World Health Organization (WHO) on the 11th March, 2020 [2].

The causative organism is Severe Acute Respiratory Syndrome Coronavirus (SARS CoV-2) [3], a beta form of coronavirus that is similar to two other coronaviruses, namely; Severe Acute Respiratory Syndrome Coronavirus (SARS CoV) and Middle East Respiratory Syndrome (MERS) coronavirus. They are single-stranded positive-sense RNA viruses reported to have caused a deadly infection in the last two decades [4].

The disease primarily spreads through contact with the fluid or droplets of an infected person, particularly via the oral, nasal, and ocular passages. In addition, it is symptomatically milder than SARS or MERS, with characteristic heterogeneous symptoms ranging from no symptoms to mild and severe symptoms [5]. The severity of symptoms is more pronounced in the geriatric population group and individuals with co-morbidities. Children present fewer clinical symptoms and the disease rarely progresses to a severe state [2].

1.1 Pathogenicity of Cytokine Storm Associated to COVID-19

A systemic traumatic condition can result due to the massive generation of chemokines and cytokines following viral infection and injuries. This condition has been reported in severe COVID-19 patients (clinical findings revealed elevated serum levels of ferritin and pro-inflammatory cytokines and reduced viral inhibiting cytokines. Similar situations have been reported in the cases of MERS CoV, SARS CoV infections and the 1997 H5N1 influenza outbreak [2].

Further, the present approach for treatment of cytokine storm relies on the use of immunomodulatory therapy (immunosuppressive). This is combined with controlling the underlying trigger (pathogen) or diseases which has the potential to produce a more favourable outcome [8, 9]. Over the years, research efforts have focused on targeting immune response with anti-inflammatory therapy in a number of severe

acute infections, including treatments with non-steroidal anti-inflammatory drugs (NSAIDs), monoclonal antibodies (MAbs), anti-cytokine and anti-chemokine agents, statins, and plasma exchange [10]. Although success has been recorded in the use of NSAIDs in treating diseases associated with inflammation [11], however, the use of other methods listed above has not been proven to be effective [12]. Moreover, long time use of these synthetic medications as immunosuppressive and immune-stimulating agents is associated with side effects including damage to gastric intestinal mucosa, kidney, heart, and effects on the immune system [11]. To overcome the negative effects of conventional medications used to treat cytokine storm, a search for natural products with little or no safety concerns as alternative treatments is essential.

2. Materials and Methods

The literature search was conducted via Google scholar, PubMed, Scopus, websites, search engines, and references from relevant articles using keywords such as: cytokine storm in Covid-19, mechanism of SARS-CoV2 pathogenesis, plants with anti-inflammatory potentials, plants with anti-inflammatory activities or properties, plants with immunomodulatory potentials, anti-inflammatory effects, and immunomodulatory potentials of *Allium sativum, Allium cepa, Aloe barbadensis, Ananascomosus, Cannabis sativa, Carica papaya, Moringaoleifera, Nigella sativa, Salvia mitiorrhiza, and Zingiber officinale*. Plants were selected and included based on literature search results and use in traditional practice. After studying abstracts and full texts of both review and research articles (published between 1994 and 2021), studies with a focus on the pathogenicity of cytokine storm, anti-inflammatory activities of each selected plant, mostly *in vivo*, a few *in vitro* studies, and one clinical trial were considered eligible and included. Duplicate materials and articles with no relevant title and abstract were carefully excluded. A total of 954 articles were screened and 88 were considered eligible for inclusion.

3. Plants with Potential Ameliorative Effects in COVID-19 Cytokine Storm

3.1 Allium sativum (Garlic)

Allium sativum (Garlic), a perennial bulb thought to be indigenous to Central Asia but now globally cultivated. Garlic is used to treat disorders such as cold, cough, asthma, heart disease, headache and tumour dating back to the ancient Egyptians' time [13]. Garlic extract was found to stimulate anti-inflammatory cytokine IL-10 in lipopolysaccharide (LPS)-stimulated human whole blood cultures, while suppressing TNF-α, IL-1α, IL-6 and IL-8 and T-cell IFN-γ and IL-2 production by monocyte [14]. Garlic powder extract has been shown to inhibit LPS-induced TNF-α and IL-1β production in human whole blood by significantly reducing pro-inflammatory nuclear factor kappa B (NF-κB) activity without affecting the production of anti-inflammatory IL-10 [15].

The comb effects of garlic extract on the upregulation of anti-inflammatory (IL-10) cytokines and the downregulation of pro-inflammatory cytokines (TNF-α, IL-1α, IL-6 and IL-8 and T-cell IFN-γ and IL-2) in LPS-induced human cells have opened the door for further research into its potential use in the fight against Covid-19.

3.2 Allium cepa L. (Onion)

Onion is a bulbous herb which belongs to the family Liliaceae and is cultivated all over the world and used as an ingredient in food and also consumed for medicinal purposes [16]. Nasri and colleagues [17] investigated the anti-inflammatory effects of onion in animals and attributed its anti-inflammatory properties to cyclooxygenase inhibition. According to Marefati and colleagues [18], onion extract significantly reduces IL-4 levels while increasing IFN-γ and IFN-γ/IL-4 ratio in Broncho alveolar lavage fluids of ovalbumin-sensitized rats. Onion and its constituent, quercetin, have been shown to suppress IL-6, IL-1β and TNF-α, and the expression of cyclooxygenase 2, NF-κB and iNOS [19]. Oliveira and colleagues [20] demonstrated the effects of onion and quercetin on suppression of inflammatory activities such as IL-4 and IL-5 in a murine model of Blomia tropicalis¬-induced asthma.
Due to the suppressive effect on cyclooxygenase, IL-6, IL-1β and TNF-α, onion can be used as an adjuvant in combination with Covid-19 antiviral treatments and clinical trials for safe use by patients need to be conducted.

3.3 Aloe Barbadensis Miller (Aloe Vera)

Aloe vera belongs to the family Asphodelaceae (Liliaceae). It is a perennial shrub, edible, and widely distributed mainly in sub-Saharan region of Africa [21]. It has a long history of traditional medical usage for treatment of wound, burns, and skin care because of its active constituents, which include vitamins, sugars, enzymes, fatty acids, minerals, anthraquinones, hormones, auxins, and gibberellins. The plant is claimed to possess strong anti-inflammatory and immunomodulatory characteristics. In the work conducted by Paul and colleagues [22], the anti-inflammatory property of aloe vera crude gel and extracts on carrageenan-induced edema in wistar rat paw was established and reported to inhibit cyclooxygenase (COX) activity and production of prostaglandin E2. A study investigated the effect of aloe vera in rat models and it was discovered to significantly lowered TNF-α and IL-6 levels [23].

3.4 Ananas Comosus (Pineapple)

Ananas comosus is the most widely known member of the Bromeliaceae family in terms of edibility. It is cultivated in several tropical and subtropical countries; it is used traditionally in several native cultures for medicinal purposes [24]. The therapeutic potential of pineapple is attributed to bromelain; a group of various

thiol endopeptidases and other enzyme mixture such as phosphatase, glycosidase, peroxidase, cellulose, and escharase derived the plant's fruit and stem (higher concentration); which contain diverse related proteins with reported in vivo and in vitro anti-inflammatory, anti-edematous, fibrinilotyc and antithrombotic properties.

In a study using human monocytic leukaemia cells and murine microglial cells, expression levels of COX-2 and PGE-2 have been demonstrated to be downregulated by bromelain [25]. In another study using stimulated immune cells, reduced secretion of TNF-α, INF-γ, IL-6 and IL-1β in inflammatory bowel disease has been observed [26]. The same was reported by Bakare & Owoyele [27] plus a reduced expression of iNOS in the sciatic nerve of laboratory rats following bromelain administration by gavage.

The reported inhibitory action of bromelain on pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) has opened a window for investigation into the possible utilisation of pineapple fruit or its extracts against COVID-19-induced cytokine storm.

3.5 Cannabis sativa (Cannabis)

Cannabis sativa, also known as marijuana or Indian hemp, is a recreational, psychoactive, medicinal, and fibre plant from the family Cannabaceae, [28]. It is an annual herb that originated from Central Asia but is globally cultivated [28]. The use of cannabis for medicinal purposes in Middle East and Asia dates back to the 6th century BCE, and was used for the treatment of rheumatism, migraine trigeminal neuralgia, tetanus, asthma, epilepsy, insomnia, and fatigue in the early 19th century [29, 30]. Δ9-tetrahydrocannabinol (THC) has been regarded as the main active constituent of cannabis [29].

THC has been shown to inhibit LPS-stimulated mRNA expression of some prion flammatory cytokines IL-1α, IL-1β, IL-6 and TNF-α at molecular level in rat microglial cells culture in cannabinoid receptors-independent manner [30]. An increase in the anti-inflammatory cytokine IL-10 was observed in the serum of mice challenged with LPS and *Corynebacterium parvum* after administration of synthetic cannabinoids WIN55, 212-2, and HU210 in an independent study in vivo [31].

Furthermore, a recent study using UV-induced inflammation in a full-thickness human 3D skin artificial EpiDermFT tissue model, Kovalchuk and colleagues [32] found that the cannabis extracts down-regulate the expression of proinflammatory cytokines IL-6, IL-1α, IL-1β, TNF-α in addition some key pro-inflammatory interleukins affected are IL-1, IL-17, IL-17C, IL-23 and IL-23A. Furthermore, the extracts of *C. sativa* cultivars significantly downregulated the NFKB2 gene expression (often invoked as a prototypical pro-inflammatory signalling pathway, the gene codes for the synthesis of "nuclear factor NF-kappa-B p100) and the levels of Toll-like receptor 2, which has been implicated in various inflammatory disorders, comprising pulmonary diseases and acute respiratory distress syndrome (ARDS) [32,33]. Additionally, the cultivar extracts showed a considerable reduction in the prostaglandin-endoperoxide synthase 2 gene expression, which codes for COX-2 [32].

The down regulatory effect exhibited by cannabis extract on the genes (NFKB2 gene and LPS-stimulated mRNA) encoding various pro-inflammatory cytokines has also made it a good candidate as an adjuvant in the treatment of COVID-19. Assessment of its safety in patients' needs to be conducted.

3.6 Carica Papaya (Pawpaw)

Carica papaya, commonly known as pawpaw, is a sweet, succulent fruit that belongs to the family Caricaceae which is cultivated across the tropical world and into the warmest parts of the subtropics [28]. Pawpaw is rich in proteolytic enzymes like papain and chymopapain, beta carotene and is known to improve all forms of digestive and abdominal disorders [34]. Different parts pawpaw are traditionally utilised to treat a variety of disorders, which include asthma, diabetes, eczema, ulcer, malaria, and typhoid coinfection [11]. An in vitro study into the anti-inflammatory effects of methanol extract of *Carica papaya* by Salim et al. [35] reveals that the extract inhibits the production of TNF-α, IL-1β, IL-6 and IL-8 in LPS stimulated human peripheral blood mononuclear cells. Also, Pathak et al. [36] reported that in aqueous extract of pawpaw seed, the flavonoid-rich fraction significantly inhibits the expression of TNF-α, IL-6, IFN-γ and NF-κB in methyl isocyanate-stimulated pancreatic epithelial cells.

Papaya and its extracts can be used in combination with COVID-19 treatment due to its inhibitory effects on TNF-α, IL-1β, IL-8, IL-6, IFN-γ and NF-κB and other nutritional importance. Furthermore, investigation on its safety for consumption by patients is necessary.

3.7 Moringa Oleifera Lam. (Drumstick)

The drumstick tree, also called horseradish tree, is a plant that is widely grown in the tropics and subtropics of Africa, Asia, and Central and South America. A member of the family Moringaceae, commonly used for nutritional and medicinal applications [37–39]. It is used to treat rheumatic and articular pains [40], as well as other inflammatory associated ailments such as cardiovascular and gastrointestinal diseases [37]. It was reported to have a variety of medicinal uses, including antibacterial, antifungal, anticancer, antioxidant, anti-inflammatory, hypotensive, diuretic, and chemo-preventive properties [37]. It was reported that in vitro, Moringa seed extract containing moringa isothiocyanate-1 significantly reduces the production of nitric oxide (NO) and the gene expression of lipopolysaccharide (LPS)-inducible nitric oxide synthase (iNOS), IL-1β and IL-6 [37]. A study by Mehta and Agrawal found that Moringa suppresses the

production of prostaglandin and leukotriene by inhibiting the enzymes COX-I and COX-II. Another study shows the effectiveness of moringa in blocking TNF-α, IL-4 and IL-6 cytokines production [41].

3.8 Nigella Sativa (Black seed)

Nigella sativa L. (*N. sativa*), also known as black seed, black caraway, or black cumin, and *Habbah al-sauda* in Arabic, is a native herbaceous plant of the Arabian Peninsula that is now cultivated in many part of the world and belongs to the Ranunculaceae family [42–44]. The plant has attracted attention of contemporary researchers for its pharmacological effects, perhaps due to the saying of Prophet Muhammad (Peace Be Upon Him) as narrated by Abu Huraira that "there is healing in black cumin for all diseases except death", and also regarded as the energizing compound of the body and as remedy for common colds, fever, headaches, and toothaches by Ibn Sina (Avicenna) in his famous book, Qanun [43, 45].

Similarly, in a previous study, when both crude fixed oil of black seed and thymoquinone (a major black caraway active compound) were administered to rats in a dose-dependent manner, a reduction in thromboxane B2 and leukotrienes B4 and C4 was observed [43].

A study by Marsik and colleagues [46] reported that quinolones from seeds of *N. sativa* potently inhibit COX-1 and 2, with thymol being more potent against COX-1, while thymoquinone and thymohydroquinone exhibit more inhibitory activities against COX-2. This goes in line with the report of El-Mezayen et al [47] based on a mouse model of allergic airway inflammation.

A result of an acute anti-inflammatory test by Al-ghamdi [42] indicated that *N. sativa* produces a significant decline in carrageenan-induced paw edoema of rats, which is comparable to that produced by aspirin. In an in vitro model of Rheumatoid arthritis, Vaillancour and collaborators [48] described the positive usability of thymoquinone in abolishing LPS-induced cytokines, including IL-1β, TNF-α, metalloproteinase-13, COX-2, and prostaglandin E2.

Because of its relevance in curing Covid-19, the inhibitory effects of *N. sativa* thymoquinone on prostanlandin E2 and IL-1β, TNF-α cytokines have made it another candidate of interest by investigators on.

3.9 Salvia miltiorrhiza (Danshen)

Salvia miltiorrhiza (Lamiaceae), commonly known in Chinese folk medicine as Danshen, is one of the most popular and well-studied Chinese herbs; its origin is traced to Japan and China and it is still among the most widely used Chinese herbs in modern Chinese clinical treatment [49]. It has been medicinally used singly or together with other herbs in treating heart and vascular diseases, Alzheimer's disease, and blood clotting abnormalities. This is due to the possession of pharmacologically important compounds, which include salvianolic acids, diterpenoid, and tanshinones [50, 51].

Furthermore, Danshen has been shown to reduce the production of LPS-induced NO, TNF-α, and monocyte chemoattractant protein-1 (MCP-1) in RAW264.7 cells in a dose-response manner, both individually and in synergy with Notoginseng radix (Sanqi) [52]. Four novel and fourteen reported compounds isolated and purified from *S. miltiorrhiza* were reported to exhibit anti-inflammatory activities with compound 4 (ethyl (2S,3R)-2-(3,4-dihydroxyphenyl)-4-((E)-3-ethoxy-3-oxoprop-1-en-1-yl)-7-hydroxy-2,3-dihydrobenzofuran-3carboxylate) demonstrating great suppression of secreted NO, TNF-α and IL-6 in LPS-induced RAW264.7 cells as well as decreasing the protein expression of iNOs and COX-2 [50].

Additionally, lipid-soluble and water-soluble bioactive components extracted from Danshen alone and in combination with sannqin, demonstrated anti-inflammatory effects in RAW264.7 cells by significantly suppressing LPS-induced NO, TNF-α and MCP-1 biosynthesis without affecting cells viability [52].

3.10 Zingiber officinale (Ginger)

Ginger (*Zingiber officinale* Roscoe) belongs to the Zingiberaceae family and is widely used as dietary condiment, flavouring agent and food and beverages spice around the world [53]. It is widely grown in warm part of Asia (such as China, and India), South America, the Middle East and Africa [54]. Gingerols and shogaol are believed to be the primary bioactive components in ginger that exert a number of pharmacological and physiological activities [53, 55]. For centuries, ginger has been traditionally used in the treatment of nausea, vomiting, colds, arthritis, and migraine [53]. Maged and his colleagues [55] reported that the anti-inflammatory effects of ginger is attributed to its capacity to reduce the production of prostaglandin E2 and nitric oxide in mouse model. The result of recent in vitro studies indicated that the primary bioactive components of ginger (gingerols and shagaols) inhibit synthesis of pro-inflammatory cytokines IL-1, IL-8, and TNF-α which is in addition to inhibiting prostaglandin and leukotriene synthesis enzymes [56]. Mahluji et al. [54] found that oral ginger supplementation lowers TNF-α and high-sensitivity C-reactive protein (hs-CRP) levels in type 2 diabetes mellitus patients' blood samples.

From what has been described by [56], gingerols and shagaols can be used as good agents against cytokine storm in COVID-19 due to their inhibitory effects on the release of IL-1, IL-8, and TNF-α, clinical investigation into the safety of this extract is necessary. In addition, all the aforementioned plants, including the bioactive agents and mechanisms of action against cytokine storm, are summarised in the Table 2.1

Table 3.1: List of Plants, Bioactive Agents and Mechanisms of Action Against Cytokine Storm

Plant	Compound	Effect
Alium sativum	Allicin	Anti-inflammatory: by stimulation of expressions of IL-10, IL-6, IL-4, T-cell IFN-γ and IL-2. Reduces inflammation: by inhibiting the actions of proinflammatory cytokines such as TNF-α, IL-1α, IL-6 and IL-8 and T-cell IFN-γ and IL-2 [14-15].
Allium cepa L. (Onion)	Quercetin	Anti-inflammatory: by suppressing cyclooxygenase, IL-4 and IL-5, IL-6, IL-1β and TNF-α activities [17-20].
Ananascomosus (Pineapple)	Bromelain	Immunomodulatory: it downregulates expression of COX-2 and PGE-2 in human monocyticleukemia cells and murine microglial cells. Anti-inflammatory: reduces secretion of TNF-α, INF-γ, IL-6 and IL-1β [24-27].
Cannabis sativa (Cannabis)	Δ^9-tetrahydrocannabinol (THC)	Suppress inflammation: by inhibiting the mRNA expression of proinflammatory cytokines IL-1α, IL-1β, IL-6 and TNF-α Suppresses the prototypical pro-inflammatory signalling pathway by the downregulation of NFKB2 gene expression and Toll-like receptor levels. Modulates inflammation by downregulating prostaglandin-endoperoxide synthase 2 gene expression, which codes for COX-2 [29-32].
Aloe barbadensis Miller (Aloe vera)	Indomethacin, Anthraquinones	Anti-inflammatory and immunomodulatory: via a significantly lowering of TNF-α and IL-6 levels and inhibits cyclooxygenase (COX) activity and production of prostaglandin E_2 [21-23].
Carica papaya (Pawpaw)	Papain and chymopapain	Anti-inflammatory: the extract inhibits the production of TNF-α, IL-1β, IL-6 and IL-8, IFN-γ and NF-κB [11, 34-36].
Moringa oleifera Lam. (Drumstick)	moringa isothiocyanate-1	Anti-inflammatory: it reduces the production of nitric oxide (NO) and the gene expression of iNOS, IL-1β and IL-6. Suppresses the production of prostaglandin and leukotriene by inhibiting the enzymes COX-I and COX-II. Blocks TNF-α, IL-4 and IL-6 cytokines production [37-39, 41].
Nigella sativum (black seed)	Quinolones, thymoquinone, thymol	Anti-inflammatory: potently inhibit IL-1β, TNF-α, metalloproteinase-13, COX-2 and prostaglandin E2 [43, 45,47].
Salvia miltiorrhiza (Danshen)	salvianolic acids, diterpenoid and tanshinones	Exhibits anti-inflammatory activities: by suppressing the secretion of NO, TNF-α and IL-6 and downregulates expression of iNOs and COX-2 [50-52].
Zingiberofficinale (Ginger)	Gingerols and shogaols	Anti-inflammatory: reduces production of PGE-2, NO, and pro-inflammatory cytokines IL-1, IL-8, and TNF-α [54-56].

4. Conclusion

The medicinal plants discussed in this review could be used alone or synergistically in the future in clinics for enhanced therapeutic effects to reduce the damaging effects of cytokine storm. Isolation of the plants' active compounds/principal agents for the study of their mechanisms of action could be explored by researchers.

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