EC PULMONOLOGY AND RESPIRATORY MEDICINE
Review Article

Promising Plant for Covid-19 Purpose: From Basic Science Understanding to Therapeutic Studies

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Abstract

Background: *Moringa* plant contains many phytoconstituents such as flavonoids, alkaloids, saponins, saccharides, glucosinolates, tannins, phenolic acids, nitrile glycosides etc. These complex natural phytochemicals contribute to its numerous physiological and pharmacological activities. COVID-19 virus SARS-CoV2 binds its receptor ACE2 and invades alveoli, nephron and other cells of the body and consequently inflammatory mediators like Tumor necrosis alpha (TNF-α), Interleukin-1 (IL-1) and (IL-6) are produced; amplified and further cellular injury will ensue. *Moringa* plants phytochemicals such as flavonoids is well known in modulation of Renin Angiotensin system (RAS) particularly by inhibiting angiotensin converting enzyme (ACE) which is the homologous of ACE2. It is also known for its inhibitory action against inflammatory mediators IL-1, IL-6 and TNF-α, inhibitory action on reactive oxygen species (ROS). Furthermore, flavonoids containing plants such as *Moringa* has anti-viral activities.

Objectives: By documenting and linking biological activities of *Moringa* plants and pathophysiology of COVID-19; it is hoped that this review will provide updated information that might help to re-purpose *Moringa* plants and other plants with similar phytoconstituents for COVID-19 and its complication.

Methods: The literatures reviewed for this paper were obtained from PubMed and Google Scholar data bases journal papers which were published from 1996 to February 2020.

Keywords: *COVID-19; Moringa; Phytochemicals; Flavonoids; Renin Angiotensin System; Inflammatory Mediators; Anti-Viral*

Abbreviations

ACE: Angiotensin Converting Enzyme; Ang: Angiotensin; AT-R: Angiotensin Receptor; COVID-19: Corona Virus Disease-2019; SARS-Cov2: Severe Acute Respiratory Syndrome Corona Virus2; IL: Interleukin; MAPK: Mitogen Activated Protein Kinase; NF-kβ: Nuclear Factor Kappa Beta; RAAS: Rennin Angiotensin Aldosterone System; RNA: Ribonucleic Acid; RNS: Reactive Nitrogen Species; ROS: Reactive Oxygen Species; SAR: Structure Activity Relationship; TLR4: Toll-Like Receptor 4; TRPV4: Transient Receptor Potential Cation Channel Subfamily V Member 4; TNF-α: Tumour Necrosis Factor Alpha

Introduction

Background

COVID-19 is an infectious disease caused by newly discovered corona virus called as Severe acute respiratory syndrome corona virus 2 (SARS-Cov2) [1]. COVID-19 was first investigated in December 2019 in Wuhan city of China [2]. Appropriate vaccine and efficient antiviral drug for human use is not prepared yet.

Up on entry of corona virus to lungs; its Spike proteins interact with receptor ACE2 on lung cells and then enter in to cells, replicate and lung injury ensues [3]. *In vivo* studies revealed that injection of SARS-CoV Spike proteins into mice worsens acute lung failure and injury can be attenuated by blocking the renin-angiotensin pathway [4].

Significant increase in AngII levels were also observed in the lung tissue of mice treated with corona virus Spike-Fc [5]. The angiotensin-I receptor (AT1-R) is the crucial receptor that mediates AngII-induced vascular permeability and severe acute lung injury [6].

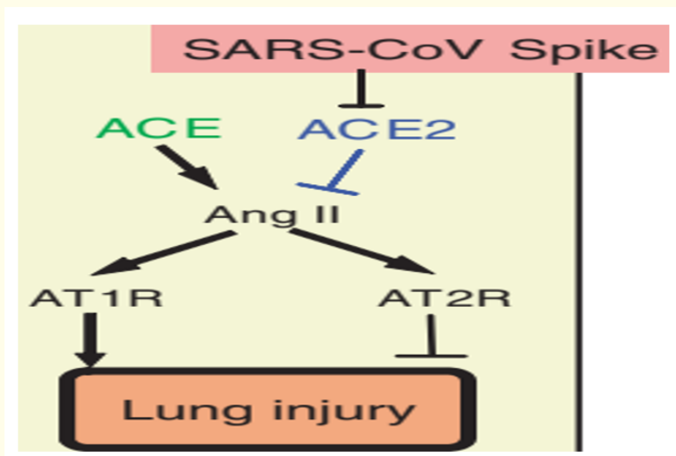

Figure 1: *Down regulation of ACE2 expression by SARS-CoV infection and SARS-CoV Spike protein [4].*
(Adopted from Work of Keiji Kuba., et al. 2005. 11(8): 875-879).

Various studies have been showing that the central to pathogenesis of COVID-19 and its complication is induction and amplification of inflammatory mediators. Cytokine dysregulation [7] and hyperinduction of pro-inflammatory mediators (IL-6 activation Plasma and TNF-α moderately up-regulation) [8] causes diffuse alveolar damage in SARS patients. Conventional wisdom suggests maladaptive systemic inflammatory immune response due to cytokine storm contributes to hypo-perfusion related to injury of renal tubules in COVID-19 and reactive oxygen species mediated acute kidney injury is observed [9].

Various extraction of *Moringa* plant leaves was analyzed to contain high amount of flavonoids and total polyphenols [10], glucosinolates [11], glucosinolates and phenolic (flavonoid-Quercetin and kaempeferol and others) [12] high content of flavonoids, glucosides, and glucosinolates [13]. Micromolar concentrations of flavonoids, such as anthocyanin, flavones, flavonols and flavanols potently modulate ACE activity [14] Inhibitory effects of flavonoids on TNF-α production is also demonstrated [15].

Flavonoids Inhibition of Lipid Mediators of Inflammation such as Eicosanoids Production including Prostaglandins, Prostacyclin, Leukotrienes, Lipoxins, Thromboxane and its Potent antioxidant activities against reactive oxygen species (ROS) and reactive nitrogen species (RNS) also determined [16]. Even some researches have revealed naturally occurring flavonoids exhibit remarkable anti-viral activity [17]. However, the possible therapeutic role of *Moringa* plant phytochemical such as flavonoids, polyphenols, alkaloids, tannins against SARS-Cov2 and its complication remains unexplained.

Methods

In order to do this updated scientific review many published experimental studies and unpublished articles will be identified and retrieved from experimental studies registration platforms, researches were searched from English electronic databases (PubMed, ScienceDirect, Google Scholar, HINARI and EMBASE) to identify the potentially relevant studies on *MORINGA* PLANT PHYTOCHEMICALS FOR COVID-19 TREATMENT PURPOSE. Manual search will be conducted by screening the reference lists of inclusive studies. The search strategy will consist the keywords used in the literature were the combinations of *Moringa* phytochemicals and associated pathophysiology of COVID-19 such as COVID-19; *Moringa*; Flavonoids; Renin angiotensin system; inflammatory mediators; phytochemicals; Anti-viral. Studies and reports with minimal importance on the topics were excluded. Finally, this review contained a total of 83 publications that are related to the title.

Study selection and outcomes

Studies which fulfill the followin criteria were included after systematically reviewing the manuscripts. The studies will be considered for inclusion if they are experimental studies; performed on experimental animals or clinical studies with COVID-19 or SARS associated with COVID 19; evaluating the potential therapeutic role of *Moringa*.

Due to feasibility, articles published in English language/have English version will be included. All above mentioned designed researches conducted experimental or clinical studies done seen emerging of SARS-CoV2 to the first day of literature search for this study will be included. Incomplete articles, reveiws, conference precedings, and duplicates will be excluded. Three authors (M.B., Z.B. and W.R) independently will screen the titles, abstracts and full-text of retrieved articles to identify their eligibility and disagreement will be judged by the others (G. H. E.K and T.G).

Literature Review

Renin angiotensin system pathway in COVID-19 pathophysiology

Coronaviruses are enveloped viruses with round and sometimes pleomorphic shapes and approximately 80 to 120 nm in diameter. Coronaviruses contain positive-strand RNA, with the largest RNA genome (approximately 30 kb) [18].

Angiotensin-converting enzyme 2 (ACE2) is receptor for SARS corona virus. Spike proteins help both for fusion to ACE2 receptor and for entry to host cells [3]. SARS pathogenesis is proposed, consisting of three phases: viral replication, immune hyperactivity, and pulmonary destruction [7].

The renin-angiotensin system (RAS) plays a critical role in maintaining normal cardiovascular physiology and is highly implicated in a spectrum of cardiovascular diseases [19]. RAS which composed of renin, angiotensinogen, angiotensin II (Ang II), Ang II receptors (AT1 and AT2 receptors), and angiotensin-converting enzyme (ACE) has become interest of scientist for search of COVID-19 drug [20-22].

Angiotensin-converting enzyme 2 (ACE2) is new homologous of ACE catalyze Ang I to Ang (1-7); while ACE catalyzes conversion of AngI to AngII. AngII is vasoconstrictor, while Ang 1-7 is a vasodilator [23]. The metalloprotease catalytic domains of ACE2 and ACE are

42% identical [24]. ACE2; a regulator of the RAS in cardiovascular disease and also plays a pivotal role in coronaviruses and influenza virus infections [25,26].

There are controversial comments regarding inhibition of RAS and its risk-benefits in SARS-CoV2. There are multiple studies supporting ACE inhibitors and ACE receptor blocker could be safely used and even can be used as target of SARS-CoV2 by degrading AngII and preventing inflammation following AngII mediated vascular injury [23,27,28]. On the other hand several hypothetical and basic sciences based studies showing that ACE inhibitors in COVD-19 leads to up-regulation of ACE2 by negative feedback mechanism and promote viral replication [22,29].

In both cases once SARS-CoV binds to its receptor, mRNA expression and the enzymatic activity of ACE2 are significantly reduced [30]. Studies done on animal model have shown that lack of ACE2 in the lung, kidneys and other organ receptor upregulate expression and accumulation of AngII [4]. AngII induced inflammatory lung injury manifested by neutrophil infiltration, Proinflammatory cytokine release and oxidative stress [23,30].

ACE2/Angiotensin-(1-7)/Mas Axis Protect against SARS induced acute lung injury and fibrosis by inhibiting the MAPK/NF-kβ Pathway. When ACE2 is abundantly occupied and inhibited by SARS-CoV2 the inflammatory pathway is amplified and lung injury might ensue [31].

Therefore, currently used immuno-modulatory drugs including anti-interleukins and anti-TNF-α will be inevitably important in treatment of COVID-19 and its sequels [32]. Additional novel potent immuno-modulatory agents are needed.

Pathophysiological mechanism involved in COVID-19 inflammation other than RAS.

Transient receptor potential vanilloid-type 4 (TRPV4) cation channel is widely expressed in all tissues as well as in immune cells and its function as mechanosensitive Ca^{2+} channel seems to be conserved throughout all mammalian species. Importantly, TRPV4 may present a missing link between mechanical forces and immune responses [33].

SARS-CoV-2 infects the pulmonary system and the majority of patients with moderate-to-severe COVID-19 suffer from ARDS. TLR4 receptors play an important role in the development of inflammatory and pulmonary vascular disease. A previous study used TLR4-deficient mice to provide strong evidence for TLR4 signaling as a mediator for pulmonary injury [34].

The TLR4-NF-kB pathway is central towards promoting infection-induced lung injury. SARS-CoV-2 infection in severe COVID-19 patients is accompanied by bacterial pneumonia. In this regard, evaluating the role played by TLR4 signaling in the lungs is critical to improving the outcomes in COVID-19 patients [35].

Cytokines are a group of polypeptide signaling molecules responsible for regulating a large number of biological processes *via* cell surface receptors [36]. COVID-19 disease leads the activation of $CD4^+$ T cells and generate GM-CSF, among others. The infection generates the secretion of several cytokines that induce inflammatory $CD14^+$ and $CD16^+$ monocytes with the consequent increase of IL-6 expression and the acceleration of inflammatory process [36].

"Flavonoids" containing plants - possibly for COVID-19 therapy

Flavonoids are low molecular weight polyphenol molecules with diphenylpropane (C6-C3-C6) basic structure in which the three-carbon bridge between the phenyl groups is usually cyclized oxygen.

Flavonoids subclasses based on the structure of the three rings- flavanols, flavanones, flavones, isoflavones, flavonols, and anthocyanins [37]. Flavonoids containing diet have been used for wide range of ailments and currently flavonoids are extensively fertile areas of research in biomedical and pharmaceutical discipline [38].

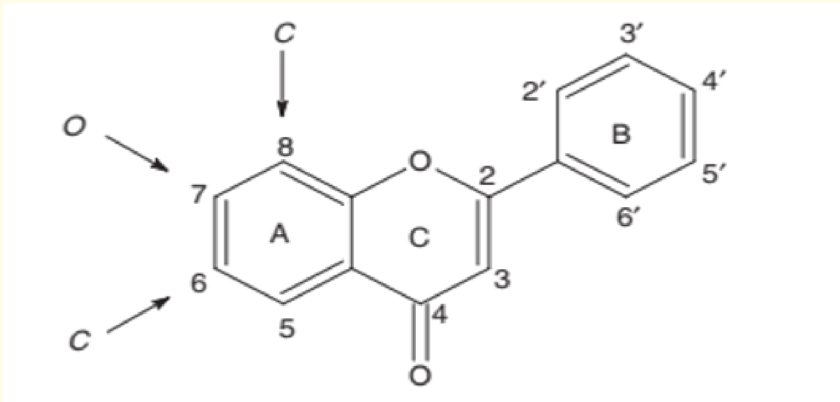

Figure 2: *General structure of flavonoids [37].*

Flavonoids are an important phytochemicals; particularly, they belong to a class of plant secondary metabolites. Plants such as *Moringa* species including *Moringa stenopetala* and *oleifera* [39-41], apple [42], wine [16,43,44], onions, garlic are some well-studied flavonoids enriched sources. Flavonoids classes in *Moringa* species and its biological actions are listed (Refer table 1).

Moringa plant phytochemical (flavonoids) immuno-modulatory activities

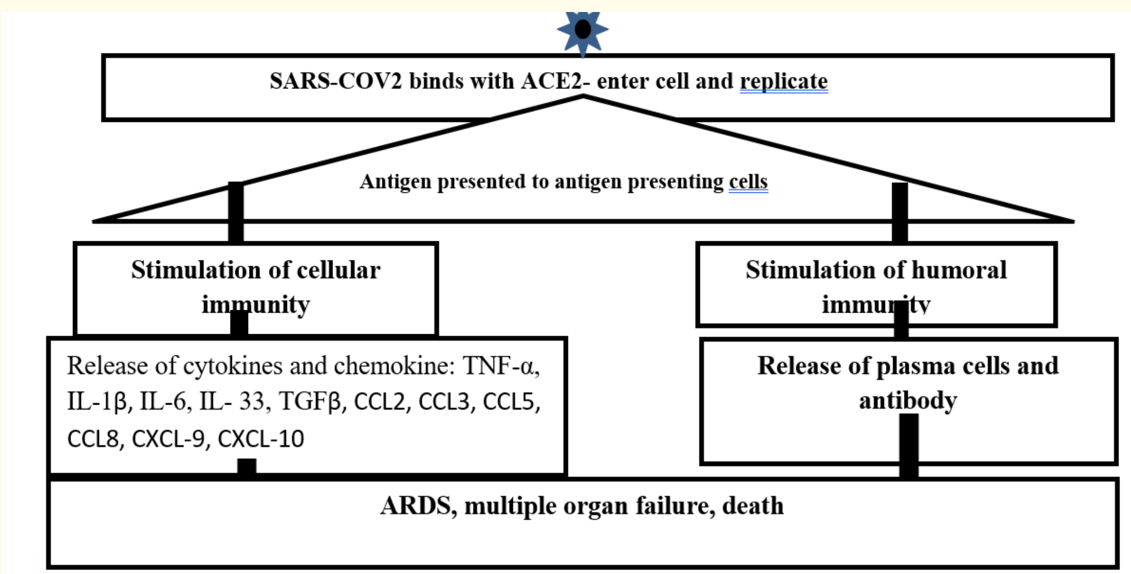

Figure 3: *Pathogenesis of COVID-19 (key: ARDS-Acute respiratory distress syndrome).*

Once activated NF-kβ promote induction of target genes inflammatory mediators cytokines (IL-1, IL-2, IL-6, Chemokines, TNF-α, TNF-β, interferon-β), inflammatory enzymes (Inducible nitric oxide synthase, Inducible cyclooxygenase-2, 5-Lipooxygenase, Cytosolic phospholipase A), angiotensinogen, and metalloproteinase [45]. NF-kβ is induced and activated up on stimulation of cells by various inducers such as, Viruses, AngII [46], reactive species (ROS) and pro-inflammatory cytokines [47]. NF-kβ promote important in cellular responses, including inflammation, innate immunity, growth and cell death.

Tocilizumab is Interleukin-6 (IL-6) receptor-inhibitors and other immune-modulating agents (e.g. alpha-interferon, sarilumab) are being used as standard protocols therapy of COVID-19 [32]. Quercetin one of flavonoids have been shown to be potent anti-inflammatory agent by modulation of pro-inflammatory gene expression dependent on Nuclear Factor Kappa β (NF-kβ) [48] and MAPK signaling [49].

Study done by Y. Tamrat., *et al*. showed methanol extraction of 400mg *Moringa* plant leaves has (53.5% inhibitory capacity) compared to 150 mg Aspirin (50.4% inhibitory capacity) of inflammation [50]. Geremew., *et al*. also determined 80% methanol extract of *Moringa stenopetala* possesses analgesic and anti-inflammatory activities [51].

The extract of *Moringa* Oleifera leaves inhibited human macrophage cytokine production (tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and IL-8), which were induced by cigarette smoke and by lipopolysaccharide [52].

Flavonoids such as apigenin, wogonin, luteolin, tectorigenin, and quercetin inhibited NO production, as measured by nitrite formation [53].

***Moringa* Species**	**Flavonoids Analyzed**	**Other Compounds**	**Biological Function**	**Reference**
M. oleifera	Quercetin, myrecytin, kaempeferol	Alkaloids, saponins, tannins, Isothiocyanates, Glucosinolates	Anti-oxidant, Anti-inflammatory, Anti-diabetic….	[54]
M. oleifera	Quercetin		ROS inhibition; Anti -hypertensive	[55]
M. oleifera	Rutin, Quercetin, kaempeferol	Saccharides and nitrile glycosides, Phenolic acids, Glucosinolates,	Anti-inflammatory and anti-oxidant	[56]
M. oleifera	Flavonoids and flavonols	Total polyphenols	Reduced TNF-α, IL-6, ROS	[57]
M. stenopetala	Flavonoids	Alkaloids, Coumarins, steroids, saponins, Terpenoids, and tannins	Diuretics	[58]
M. oleifera	Quercetin	Phenolic, lipids	Anti-oxidant; free radical scavenging	[59]
M. concanensis	Crude extract	Crude extract	Potent Anti-oxidant; ROS i nhibition	[60]
M. oleifera	Quercetin, kaempeferol, apigenin		Antioxidant and anti -inflammatory	[61]
M. peregrina	Phenol	Phenol	Anti-oxidant	[62]
M. oleifera	Flavonoids	Other phenols	Anti-oxidant (free radical scavenging)	[63]

M. oleifera	Quercetin glucoside, quercetin rhamnoglucoside (rutin) and chloro- genic acid.		high antioxidant; radical scavenging effects	[64]
M. oleifera		Carbohydrate, ascorbic acid, fibers, protein, iron, calcium, vitamin, potassium, magnesium and vitamin	Nutrient	[65]
M. stenopetala	Rutin, quercetin, kaempeferol	Other phenolics and glucosinolates	Anti-oxidant	[66,67]

Table 1: *Review of phytochemicals in Moringa species and its biological activities.*

Moringa plants phytochemical (flavonoids) modulates RAAS

Studies shown different flavonoids, such as anthocyanins, flavones, flavonols, and flavanols, have been shown to potently inhibit ACE activity [14]. Inhibition of metallopeptidase which is catalytic site of ACE and ACE2 by flavonoids and other phenolic compounds is also determined [68]. Anti-hypertensive action of flavonoids is due to Anti-oxidant and ACE inhibition action of flavonoids [69].

Structure-activity relationship (SAR) is responsible for flavonoids biological function; the position and number of substituents in its basic structure significantly affects functions. Double bonds reactivity, methoxylation, hydroxylation and glycosylation capacity of flavonoids with ACE is associated with its unique structure [14,68].

ACE inhibition by flavonoids of plants like *Moringa* stenopetala then downregulate the production of AngII; thus might attenuate AngII induced cell injury and inflammation of lungs, kidneys and other organs caused by COVID-19.

Flavonoids Class/Subclass	Action	Reference
Flavan-3-ols and procyanidins	ACE inhibition	[70]
Flavonoid-rich fraction	ACE inhibition, Free radicals scavenging	[71]
Flavonoids	Anti-oxidant and free radical scavenging detoxifying	[72,73]
Flavonoids	Increase Nitric oxide bioavailability	[74]
Flavonoids	ACE inhibition, reduce inflammation and ROS	[75]
Flavanols	ACE inhibition	[76]
Flavonoids	ACE inhibition	[77]
Luteolin, kaempeferol, quercetin, Catechin naringenin.	COVID-19 protease docking [inhibition]	[78]
Quercetin, kaempeferol, Luteolin	ROS inhibition, ACE modulation	[79]
Proanthocyanidins	Free radical scavenging, ROS inhibition	[80]
Flavonoid	Reverse AngII induced cardiac hypertrophy by NO release oxide release	[81]

Table 2: *Review of flavonoids and biological actions [RAAS inhibition, inflammation modulation].*

Moringa plant phytochemical (flavonoids) anti-viral activities

Since the 1940s many reports show that naturally occurring flavonoids exhibit a remarkable anti-viral activity [17]. Flavonoids such as myrecitin, quercetin, kaempeferol and Luteolin have shown top possess antivirus activities against murine norovirus [82]. Like corona virus; Noro virus is a class of single stranded RNA virus. (E)-2-styrylchromones an emerged new class of flavonoid compounds have potential anti-noro virus anti-rhinovirus activities [53]. Plants rich in polyphenols have been used to cure various virus, bacterial and fungal disease [83].

Conclusion

Natural compounds have been the center of attention among researchers working in pharmacology and Bio-medicals due to their high availability and low side effects. Phytochemicals Flavonoids which is abundantly found in our daily vegetables and fruits such has been studied for decades for its significant promising therapeutic importance in viral diseases.

Moringa plant which is commonly used as cabbage in southern Ethiopia has been also traditionally consumed for diverse diseases from oncology, cardiovascular disease to anti-inflammation. It is well known for its richness in flavonoid compounds and other abundant pharmaceutically active ingredients.

Pathophysiology of COVID-19 is complex and involves multiple mechanisms like Transient receptor potential vanilloid-type 4 (TRPV4) cation channels, TLR4 receptors, Cytokines, chemokines and more group of polypeptide signaling molecules, and we focused in this mini-review on RAS pathway as pathophysiology of COVID-19 is more orchestrated by Renin angiotensin system (RAS) pathway particularly by virus interaction and activation with Angiotensin converting enzyme2 receptor (ACE2) which is followed immuno-dysregulation. Biological activities of phytochemicals such as flavonoids including RAS modulation and immuno-modulation (anti-inflammatory, anti- oxidant) and furthermore anti-viral activities might have promising therapeutic importance in COVID-19.

Future Direction

This conceptual and empirical science based review expose a number of interesting future research opportunities regarding alternative ethno-medicine study for COVID-19 and similar multidisciplinary areas. First, engagement in re-purposing already studied modern and traditional medicine in the midst of this tough time where no appropriate vaccine or drug available is economic and life-saving during this global pandemic.

Second, applying evidence based complementary and alternative medicine in this urgent time when any definitive and supportive care has great value is inevitably important. As part of this, studying and making inference that *Moringa* and other similar dietary component may have some therapeutic purpose in COVID-19 is significantly important; because expected adverse effect will be minimal and therefore 'reverse pharmacology' study could be applied instead of extensive and time taking traditional method of drug development.

Future researches may invest time in developing a better understanding whether medicinal plants like *Moringa* has little benefit in COVID-19 or equally important, if no benefit. These future research venues, along with this kind of researches, will advance 'basic science based therapeutic finding' as an exciting area of research with ample opportunities for future exploration.

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