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An Update on Herbal Bioactive Phytochemicals and their Potential Role during the COVID-19 Pandemic: A Review

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Abstract: The current COVID-19 pandemic is the main issue globally, and finding solutions either for disease prevention or treatment is nowadays a key scientific concern. Good immunity can be shown as the only proven method of overcoming or minimizing the adverse effects of virus infections. Since Coronavirus spread, different conventional herbs were used as a traditional medication to enhance people's immunity to combat the virus. Herbs are sources of several phytochemical compounds with compelling bioactivities. A review of the studies concerning herbal plants with proven properties against viral infections is highlighted in the present work. Besides, this work also contains some of the recently published studies related to natural herbs that could be highly beneficial in preventing or treating the infection by Coronavirus. Based on the reviewed literature presented in this update, it was concluded that phytochemical constituents found in many herbs could have a potential role in preventing or treating the symptoms associated with Coronavirus infection.

Keywords: Bioactive compounds; COVID-19, Antiviral, Herbal therapeutics.

Introduction

The pandemic disease novel Corona (COVID-19) had its origin in the Wuhan District of China (Hubei Province). The novel Coronavirus is a life-threatening disease if not taken care-off; that has spread globally with no conventional treatment. Since ancient days, human health has been critically impaired by viral infections (Pereira & Critchley, 2020). Nowadays, a continued epidemic of COVID-19, a new coronavirus, SARS-CoV-2, triggered in December 2019 in Wuhan, China, is affecting world health (Tahir *et al.*, 2020).

Since the virus has still no treatment, immunity must play a key role in preventing viral infection. The immune system is the best body's protector. It is the body's defense to protect against all pathogens (such as viruses). An infection like COVID-19 stays unchecked as long as the immune system functions normally (Chowdhury *et al.*, 202). Coronavirus (Family: Coronaviridae) have an enveloped virions (virus particles) that measure roughly 120 nm in diameter are positive-stranded Ribonucleic acid (RNA) viruses with the

largest genome, typically extending from 27 to 32 kb. Club-shaped glycoprotein spikes in the envelope give the viruses a crown-like appearance. The nucleo-capsid, made up of a protein shell identified as a capsid and comprising the viral nucleic acids, is helical or tubular. SARS-CoV-2 is a non-segmented, single-stranded positive-sense RNA virus having pikes on the outer surface (Pal *et al.*, 2020), as illustrated in fig. (1). There are three structural proteins linked with the virus: membrane protein, envelope protein, spike protein, while encrypting into an enclosure linked to the hemagglutinin-esterase protein. The membrane protein and envelope protein are part of virus assembly, while the spike protein facilitates virus entry into host cells. The coronavirus genome consists of a single strand of positive-sense (RNA) (Gagan *et al.*, 2021).

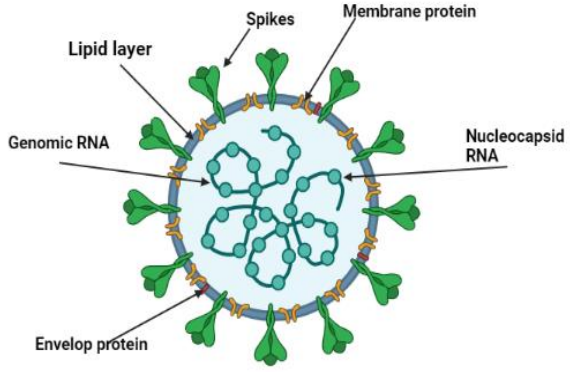

Fig. (1): Schematic structure o COVID-19 (Created with BioRender.com)

The worldwide spread of Covid-19

In early December 2019, many cases were detected with pneumonia, with an unidentified cause first emerged in Wuhan, Hubei province of China. This was referred to as Wuhan Virus (WHO Timeline, 2020). Later, it was confirmed as a public health emergency by the World Health Organization (WHO) which named it Coronavirus disease 2019 (COVID-19) in early January 2020. Among the viral infections, the most recent human AVs (HCoV) connected with the epidemic of coronavirus (SARS-CoV), and the Middle Eastern Respiratory Syndrome (MERS-CoV) have produced acute respiratory distress syndrome (Sharma *et al*., 2020). As most of the studies worldwide implicate, that virus originated from China and spread well beyond China, worldwide to close to 221 countries and territories (Michael *et al.*, 2020).

Coronavirus 2 (SARS-CoV-2) widely spreads through contact and air droplets. The spread of the virus can be tracked using technology such as A.I., machine learning that can identify high-risk patients and treat patients in real-time. A.I. can predict by population screening samples data the prediction for the patient's risk of mortality (Sarkar & Chavali 2020). A transmittable disease COVID-19 (Coronavirus disease 2019) is instigated by coronavirus 2 (SARS-CoV-2 or SC-2), an extreme acute respiratory syndrome. Many countries have been affected due to the transmission of SC-2, with a vast volume of dismissing to date.

Globally, by the end of February 2021, there have been 111,593,712 confirmed cases of COVID-19 and continuing with different strain infections, with 2,475,040 deaths as received by WHO from national authorities (Naz *et al.* , 2021). Fig. (2) gives the spread of novel Coronavirus confirmed infections around the world.

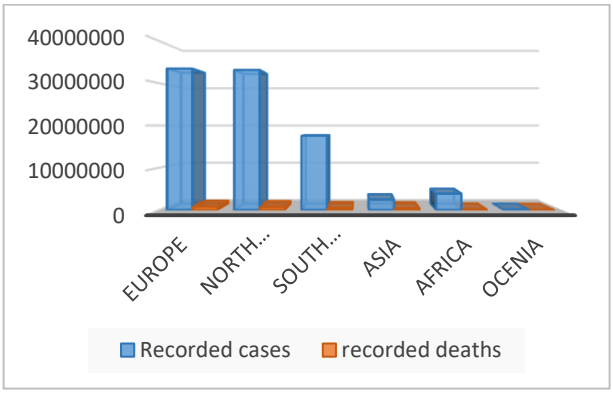

Fig. (2): Distribution of Covid-19 cases and deaths (Roser *et al.*, 2020)

Viral epidemics are prevalent in the environment. The current situation stresses the need to bring an effective and safe sensor to detect viruses present in the environment and living bodies. Our existing technology and medical facilities need to utilize together in terms of nanomedicine (Vishal *et al*., 2021), bioactive compounds, and natural products to control the situation. The search for new drugs with potential biomedical importance from botanical sources has expanded during the last 50 years. During the same period, human intervention has negatively affected the biodiversity of geographical areas where these plants are often found. In this update, we have provided an assessment of the available natural compounds (phytochemicals) as potential therapeutic agents against coronavirus complications. Safe defensive bioactive compounds and new active medical solutions obtained from particular day to day valuable herbs with antiviral properties were revealed. Fig. (3) gives some bioactive compounds from selective herbs that could combat against COVID-19.

Fig. (3): Some phytochemicals from herbs

Bioactive phytochemicals

Natural phytochemicals with potential immune-stimulating activity include terpenoids, phenolic compounds, flavonoids, alkaloids and polysaccharides (Venkatalakshmi *et al*., 2016). For years, traditional herbal medicine proved its effectiveness in treating people. Herbal bioactive phytochemicals have been spotted through many studies as immunity-boosting agents. It is generally agreed that any material's antioxidant, immune-modulatory and anti-inflammatory activities are closely related (Grigore, 2017). In this context, herbs may possess antiviral properties owing to their phytochemical constituents. The WHO has realized that herbal medicine's health advantages can help in protecting the world population's health through traditional medicine (Saxena *et al*., 2021). Several studies have reported the potential role of herbs with different bioactive phytochemicals in combating many types of viruses. For example, the Chinese herb *Artemisia capillaries* showed anti-HBV activity against the hepatitis virus (Geng *et al*., 2018).

The two herbs *Dryopteris crassirhizoma* and *Morus alba* were identified as inhibitors for viral replication of the Dengue virus (Maryam *et al*., 2020). Aloperine alkaloid isolated from a Chinese herb (*Sophora alopecuroides*) was shown to inhibit the propagation of the hepatitis C virus (Lv *et al*., 2020), inhibited replicating the influenza-A virus were identified in *Paeonia lactiflora* Pall's aqueous extract (Zhang *et al*., 2020). *Portulaca oleracea L.* effectively alleviates the signs and symptoms of influenza A virus infection (Li *et al*., 2019). The entry of the ZIKA virus was blocked and prevented by tannic acid isolated from *Terminalia arjuna* (Li *et al*., 2019). Saponin from the herb *Abrus cantoniensis* was reported to efficiently suppress the propagation of the hepatitis-B virus (Yao *et al*., 2020). The compound "forsythoside "obtained from the herb *Forsythia suspense* inhibited the virus of influenza A by viral M1 protein reduction (Law *et al*., 2017).

In 2020, many researchers have directed their work towards COVID-19 studies. In this context, many studies were devoted to exploring the possible role of natural herbs in this battle against COVID-19. Law *et al.* (2020) published a discussion about *Artemisia annua* herb and its active ingredient Artemisinin. The authors suggested that this traditional Chinese herb may combat COVID-19. They based their assumption on a previous study that showed that Artemisinin can treat severe acute respiratory syndrome Coronavirus (SARS-CoV) (Law *et al*., 2020). Fujimoto & Isidoro (2020) reviewed the potential of different herbs as a potential candidate for Coronavirus inhibition based on the fact that there is an 80% homology between SARS-CoV-1 and SARS-CoV-2 (Fujimoto & Isidoro, 2020). The Chinese herbs or fungi: *Discorea batata* (Shanyao), Spreading *Hedotis diffusa (*Baihuasheshecao*)*, Root of snow of June (*Baimagu*), *Astragalus propinquus* (Huangqi), *Wolfiporia extensa* (fulin), and *Cornus officinalis* (Shanzhuyu) were investigated for their active ingredients that could protect the kidney against renal injury that appears in patients with Coronavirus disease (He *et al*., 2020). In India, '*Ayush* Kwath' a mixture of four herbs (basil, cinnamon, ginger and black pepper) was recommended for immunity boosting during the COVID-19 pandemic (Gautam *et al*., 2022).

It was also reported that five Chinese herbs: *Bupleurum* spp. (Chaihu), *Puerariae lobata* (Gegen), *Puerariae thomsonii* (Gehua), *Cyathula officinalis* (Chuan niu xi), *Hemerocallis radix* (Xuancaogen) with quercetin and kaempferol as main bioactive compounds could be good anti-SARS-CoV-2 (Boyu *et al*., 2020*).*

Lee *et al.* (2021) conducted a systematic survey on various Chinese herbal preparations to review their bioactive constituents and their efficacy against COVID-19. It was concluded that some herbal formulas showed excellent relief of two characteristics of COVID-19 infection, which are lung congestion and diarrhoea (Lee *et al*., 2021). Baicalein, the bioactive ingredient of the medicinal herb *Scutellaria baicalensis* Georgi was proved to prevent SARS-CoV-2 cell damage and enhanced VeroE6 cell morphology to 0.1 μM and above (Song *et al*., 2021). Mu *et al.* (2021) observed that certain possible Rhizoma Polygonati compounds such as diosgenin and (+)-Syringaresinol-O-beta-D-glucoside could

have a high potential in the treatment of COVID-19 for a variety of different targets with viral and cancer-specific signals (Mu *et al*., 2021).

Few scientists analysed and established main objectives for the respective pathways and possible active ingredients for those herbs for the effect of 578 herbs and all 338 traditional Chinese medicinal herbs recorded anti-COVID-19 formulations on the cytokine storm-related signalling pathways (Dai *et al*., 2021). Gowrishankar *et al.* (2021) concluded that phytochemicals from some Indian traditional herbs with the implication in steam inhalation therapy would be promising in fighting the Coronavirus. Several kinds of herbs were reported to exert different types of bioactivity, as given in table (1).

Pharmacological potential

Plants produce several and assorted varieties of organic bioactive compounds that may differ in quantity and quality for a given species of plant growing in different regions. They often accumulate in smaller quantities and have a significant role in several developmental stages of the plants; they can also display significant therapeutic potentials. In the broad sense, the active compounds include flavonoids, alkaloids, phenolics, saponins, tannins and terpenoids (Altemimi *et al*., 2017).

Varying biological effects are exhibited by flavonoids such as anti-inflammatory, antiallergic, anti-tumour, anti-hepatotoxic, anti-ulcer, antiviral actions and a potent water-soluble antioxidant. It scavenges free radical and prevents cells from oxidative damage. They even influence biochemical reactions inhibiting certain enzymes and hormones (Mills & Bone, 2000; Narayana *et al*., 2001). From earlier studies conducted by Eid & Haddad (2017), it is known that quercetin is one of the most promising bioflavonoids effective against cancer, inflammation, obesity, cardio-diseases and metabolic disorders. Also, plant alkaloids have an essential function in treating and curing autoimmune disorders (Khan & Gerber, 2020). Thus flavonoids and alkaloids in combination act as a noble compound against antiviral and antibacterial diseases (Kaur, 2014). Flavonoids and phenolic molecules together show effective actions against microbial invasion and prevent cellular injuries (Mondal *et al*., 2009). Saponins have several biological actions such as regulating cell membrane permeability (Hostettmann & Marston, 1995), reducing cholesterol levels (Francis *et al*., 2002), immunomodulatory effects (Sun *et al*., 2009), antimicrobial activity and cytotoxicity potential (Bachran *et al*., 2008; Thakur *et al*., 2011). Altogether saponins and tannins have an impressive effect as anticancer and antiviral agents (Yildirim & Kutlu, 2015).

Biologically active terpenoids can be categorised into monoterpenes, diterpenes, triterpenes, sesquiterpenes, and a broad range of pharmacological potentials anti-carcinogenic, anti-inflammatory, anti-coagulative and immunomodulatory effects (Paduch *et al*., 2007) and acting against several infectious diseases caused by viruses, bacteria and fungi.

Phenolics play an important part as a potent antioxidant; they are free radical scavengers and have metal-chelating attributes (Soobrattee *et al*., 2005). Among various essential oils (EOs), eugenol is largely responsible for

Table (1): Selective herbal compounds and their potent bioactivities

Plant name (Botanical Name)	Family	Major Bioactive Compound	Bioactivity	Reference
Ginger (*Zingiber officinale*)	Zingiberaceae	Gingerol	Antioxidant, anti-inflammatory, antifungal, anti-cancerous, neuroprotective, antimicrobial and antiemetic	(Mao *et al*., 2019)
Thyme (*Thymus vulgaris*)	Lamiaceae	Thymol	anti-inflammatory, antioxidant, antimicrobial, and antiseptic	(Lorenzo *et al*., 2019; Nieto, 2020)
Coriander (*Coriandrum sativum*)	Apiaceae	Linalool	Hypoglycemic, hypolipidemic, analgesic, anti-inflammatory, antimicrobial, anti-oxidising and anti-caustic, anticancers and antifungal	(Laribi *et al*., 2015)
Lemongrass/ Citronella (*Cymbopogon citratus*)	Poaceae	Citral	antiseptic, anti-fever, anti-dyspeptic, anti-inflammatory and analgesic	(Olorunnisola *et al*., 2014)
Clove (*Syzygium aromaticum*)	Myrtaceae	Eugenol	Antioxidant, antimicrobial and antiviral	(Olorunnisola *et al*., 2014)
Chamomile (*Matricaria chamomilla*)	Asteraceae	Apigenin	Antioxidant, antifungal, and antitumor activities	(Farideh *et al*., 2010; Osman *et al*., 2016)
Black Cumin (*Nigella sativa*)	Ranunculaceae	Thymoquinone	Anti-inflammatory, antimicrobial, and immune-stimulatory activities, antiviral compounds	(Koshak & Koshak, 2020)
Black pepper (*Piper nigrum*)	Piperales	Piperine	Antioxidant, antimicrobial, anti-inflammatory, gastro-protective, and antidepressant	(Butt *et al*., 2013)
Turmeric (*Curcuma longa*)	Zingiberaceae	Caleb in-A	Antioxidant, anti-inflammatory, anti-mutagenic, antimicrobial and anticancer	(Aggarwal & Harikumar, 2009; Wright *et al*., 2013)
Fennel (*Foeniculum vulgare*)	Apiaceae	*Anethole*	Anti-inflammatory, analgesic, carminative, diuretic and antispasmodic agents	(Ahmed *et al*., 2019; Belabdelli *et al*., 2020)
Cinnamon (*Cinnamomum verum*)	Lauraceae	Cinnamaldehyde	Antimicrobial, antifungal, antiviral, antiallergic, antitumor, antilipemic, antidiabetic, antipyretic, antiulcerogenic, antihypertensive, gastroprotective, and immunomodulatory and anaesthetic	(Gulcin *et al*., 2019)

curing various ailments related to gastric disorders, heart complications, metabolic abnormalities and many more (Prakash & Gupta, 2005).

Mechanisms of virus inhibition

The inhibition of virus by phytochemical constituents have several mechanisms. Some phytochemicals may act by inactivating the host enzyme of the virus and others may inhibit the phosphorylation of protein and thus restricting the virus replication (Ghildiyal *et al*., 2020).

Conclusion

The COVID-19 pandemic has led to a surprising loss of lives and economy across the world. Still, the spread of the virus is not stopping, and the number of cases and mortality due to it is increasing daily. To present, there are a limited number of pharmaceutical products proven to be effective against COVID-19. Herbs have interesting antioxidant, anti-inflammatory, and immune-modulating properties that make them excellent candidates for combating the "Corona" virus by boosting immunity and potentially improving the general health of patients or alleviating the disease symptoms. In this context, herbal plants based on their phytochemical bioactive ingredients may be used as effective antivirals against SARS-CoV-2 or preventive agents.

Applying technologies like A.I can leverage this situation through its applications in various public awareness, early detection and diagnosis during the infection, contact tracing, monitoring the treatment, drug discovery and vaccine development. AI can be powered to screen trillions of compounds and establish models to predict rapid diagnosis and treatment. The usage of emerging technologies with integrative medicines with AI accelerates the revival of the pandemic situation in a manageable way. In addition to herbal bioactive compounds, AI tools can be used to search and predict a narrowed list of drug components that can be clinically tested later.

The world is growing fast to fight against the novel virus effectively. However, there is a strong need for global commitment to support research and development in this field.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work.

Ethical Statement

This paper did not perform any experimental research either on humans or animals.

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تحديث عن المواد الكيميائية النباتية النشطة حياتيا ودورها المحتمل خلال جائحة كوفيد-19: بحث مراجعة

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المستخلص : تعد جائحة COVID-19 القضية الرئيسية على مستوى العالم ، ويحاول الكثيرون إيجاد حلول إما للوقاية أو العلاج الذي يمثل الشاغل العلمي الرئيسي. ونجد ان المناعة الجيدة هى الطريقة الوحيدة التي أثبتت جدواها للتغلب على الآثار الضارة للعدوى بالفيروس أو التقليل منها. منذ انتشار فيروس كورونا، تم استخدام الأعشاب التقليدية المختلفة كدواء تقليدي لتعزيز مناعة الافرد لمكافحة الفيروس. وتعد الأعشاب هي مصدر للعديد من المركبات الكيميائية النباتية ذات الأنشطة الحيوية الهامة. ويستعرض العمل الحالي مراجعة للدراسات المتعلقة بالنباتات العشبية ذات الخصائص المثبتة ضد الالتهابات الفيروسية. إلى جانب ذلك، يحتوي هذا العمل أيضًا على بعض الدراسات المنشورة مؤخرًا المتعلقة بالأعشاب الطبيعية التي يمكن أن تكون لها اثار مفيدة في منع أو علاج الإصابة بفيروس كورونا. بناءً على الدراسات التي تمت مراجعتها والمقدمة في هذا البحث، وجد أن المكونات الكيميائية النباتية الموجودة في العديد من الأعشاب يمكن أن يكون لها دور محتمل في منع أو علاج الأعراض المصاحبة لعدوى فيروس كورونا.

الكلمات الداله: مركبات نشطة بيولوجيا كوفيد -19 مضاد فيروسات؛ العلاجات العشبية.