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Review Article

Analysis of Bioactive Compounds for the Management of Covid-19

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Abstract

COVID-19 is an infectious disease caused by SARS-COV-2. The infection due to corona virus is disseminating persistently across the globe and the exponential hike witnessed in the number of cases evinces it to be one of the massive disasters in the history of mankind. Due to the inadequacy of specific treatment and/or vaccine, a global response is urgently required so as to fulfill the need of discovering potent drugs against the unusual widespread disease. Synthetic drugs, such as hydroxychloroquine, have attained certain recognition. Nevertheless, the effectiveness of repositioned drugs is still under consideration though some acute side-effects are a cause of concern. This highlights the seriousness to come about with novel drugs which determines to offer efficacious results and is functional at low-risk. Bioactive compounds can help solve the purpose as these products are beneficial in the development of drugs or accessory therapy of such infection. These compounds can exhibit its activity either as inhibitory agents or treatment catalysts. Natural products are reported to be incessant as bioactive substances and some phytochemical classes such as flavanoids, alkaloids and phenols. Various evidences have been reported in the literature concerning the efficiency of bioactive substances available in nature and this review further intends to provide a frame of reference on the potentiality to utilize it as a commencement for the expansion of novel approaches against the stated viral infection.

Keywords

Covid, Bioactive, Pandemic, Natural Products.

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Introduction

Viral infections are presently regarded as a persevering public health concern. A virus can be defined as a sub-microscopic, an infective agent which holds the capability to multiply only within the living cells of a host. This entity is typically composed of a nucleic acid molecule in a protein coat which is thereby accountable for causing illness. COVID-19 is a viral disease caused by a novel acute respiratory syndrome (SARS-CoV-2) (Anuj Kumar, 2020)which has given rise to a pandemic. This prevalent widespread disease is speedily expanding with distinct morbidity and mortality, resulting in a considerable socio-economic impact (S. Udhaya Kumar, 2020) (Dharmendra Kumar, 2020). SARS-CoV-2 is known to be the human strain of the Coronoviridae family belonging to a major class of single-stranded enveloped RNA viruses which utilizes both mammals and reptiles as their hosts including bats and snakes (Manoj Kumar Gupta, 2020). The name SARS-CoV-2 has been designated to this virus because of 82% similarity in RNA genome to the former SARS coronavirus (SARS-CoV); both of which belong to the genus betacoronavirus. The exponential rise in the number of cases has been observed as a result of human-to-human transmission (Angeliki M. Angelidi, 2020) (Mao Wang, 2020). People infected with COVID-19 virus will encounter mild to moderate respiratory illness and recover without

requiring any special treatment (COVID-19 Disease due to SARS-CoV-2 (Novel Coronavirus), 2020). Older individuals and those with underlying medical complications such as cardiovascular disease, diabetes, chronic respiratory disease and cancer are more likely to develop serious illness (Liqiang Ni, 2020). The COVID-19 virus outspreads, in general, through droplets of saliva or discharge from the nose when an infected person coughs or sneezes (Mason, 2020), thus it is predominant to practice respiratory etiquette (For example; by coughing into a flexed elbow) (Israel Júnior Borges do Nascimento, 2020). The diagnosis of SARS-CoV-2 infection relies on qualitative Real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) analysis on a nasopharyngeal swab (Rio, 2020) (Amber Ather, 2020). Nonetheless, the presence of this virus has also been illustrated in further tissues, encompassing sputum, faeces, bronchoalveolar fluids and blood with distinct viral kinetics (Amit R. Singh, 2020).

The principal viable targets of SARS-CoV-2 virus encompass papain-like protease (PLpro), 3-chymotrypsin-like protease (3Clpro), spike (S) proteinsand RNA-dependent RNA polymerase (Yanfang Xiana, 2020). Until now, there are no antiviral drugs or vaccines against betacoronaviruses counting SARS and MERS (Nakarin Suwannarach, 2020). Nevertheless several synthetic compounds revealed favourable activities encompassing chloroquine phosphate and hydroxychloroquine in the course of early stages of infection. Novel antiviral medicines such as lopinavir, remdesivir, azithromycin, favipiravir, ribavirin, arabidol, interferon, convalescent plasma, steroids and anti-IL -6 inhibitors showed remarkable recovery for infected cases or subjects (Farhana Rumzum Bhuiyan, 2020). However, a number of detrimental effects such as acute pancreatitis, neutropenia, hepatitis and anaphylaxis have been reported, especially in patients treated with chloroquine/hydroxychloroquine, azithromycin and lopinavir-ritonavir (Australian Commission on Safety and Quality in Health Care, 2020). Therefore there is an urgent need to figure out an approach that must be both effective and safe to face this extremity. Natural products are incessantly regarded as a proliferous originator of drug leads, incorporating those isolated from marine ecosystems highlighting exceptional biological and chemical diversities (Valter R.M. Lombardi, Volume 3 Issue 1,2018). A considerable amount of bioactive compounds have been alienated and were revealed to possess antioxidant, anti-inflammatory, cytotoxic and antimicrobial properties as well.

During human history and evolution, natural products play an indispensable role in the advancement and treatment of various diseases. Essential oils and extracts procured from plants and animals are accounted as a considerable originator of bioactive metabolites (Bui Thi Phuong Thuy, 2020). Bioactivities of natural products are being comprehensively utilized in pharmaceutical industry and ethnobotany, for instance, inflammation, cancer, oxidative stress and several viral infections (Teodoro, 2019). A divergent number of antiviral bioproducts have already been traced due to exhibition of their activity against Dengue virus, Coronavirus, Enterovirus, Hepatitis B, Influenza virus and HIV. Consequently, bioproducts could act as a boon companion in the fight against SARS-CoV-2 via facilitating the expansion of specific therapies counter to COVID-19.

Inoculation And Replication of Sars-Cov-2

The genomic sequence of SARS-CoV-2 accredited the recognition of the key proteins and various enzymes intricated in its inoculation and replication activities. Providentially, its genomic sequence nearly bears a resemblance to SARS-CoV-1 (79.5%) and sole strain of coronaviruses which is only epizootic in bats (96%) (Harapan Harapan, 2020). The genomic data clearly illustrates that viral replication and inoculation of SARS-CoV-2 in humans (host) arises chiefly via three crucial proteins and enzymes. These proteins comprise of papain-like protease (ACE2), spike protein (TMPRSS2) and the 3-chymotrypsin-like protease (3CLpro) (Ni Putu Linda Laksmiani, 2020).

In the midst of these three structures, the ACE2 and TMPRSS form a proportion in the host cell. The angiotensin-converting enzyme type 2 (ACE2) looks alike to the angiotensin-converting enzyme type 1 (ACE) and a segment of the renin-angiotensin system is accountable for regulation of blood pressure (K.Rajamaheswari, 2020). Nearly all the drugs and therapies emerging as active against COVID-19 have been generated keeping in consideration, the ACE2 inhibition, however working on such a central pressure control system is in all likelihood not the best strategy to opt. The spike protein with which SARS-CoV-2 interacts (TMPRSS) is the transmembrane protease serine type 2. It was evaluated that in the wake of SARS-CoV-2 binding with ACE2, host TMPRSS2 stimulates fusion of virus with the infected cell and its activation by cleavage of virus protein. Eventually, the 3CLpro is amenable for the proteolytic cleavage of virus polypeptide in 11 non-structural proteins accountable for its replication (Muhammad Tahir ul Qamar, 2020). Hence occurrence of 3CLpro only within SARS-CoV-2 and not in the host cell dragged heed as an attainable inhibition site for COVID-19 treatment expansion.

The relatedness of SARS-CoV-1 and SARS-CoV-2 can serve as a short-cut in a specified treatment growth for COVID-19 as well as a "universal" treatment for the infection caused by this virus, as a substantial deal of research has already been conducted based on these coronavirus strains (Yang Yang, 2020). Bioactive compounds are therefore considered precious for invention of drugs and adjuvant therapy of such infection. These composites can act either as prophylactic agents or treatment activators (Preeti Sharma, 2017). Naringin (a flavanone-7-O-glycoside with possible inhibition of COVID-19 binding

to ACE-II receptors), Naringenin and Hespertin (flavanone), Hesperidin (flavanone glycoside), Baicalin and Neohesperidin (flavone glycoside), Nobiletin (O-methylated flavone), Scutellarin (a flavone), Nicotinamide (non-proteinogenic amino acid), Glycyrrhizin (Saponin) and Emodin (6-methyl-1, 3, 8-trihydroxyanthraquinone) are nearly substantial natural ACE-II inhibitors (Lovnish Thakur, 2020).

The precluding influence of Naringin on proinhibitory cytokines (intensified in COVID-19 infection) together with Cyclooxygenase-II, Interleukin-6 and -1ß and Nitric oxide synthase is significant. Glycyrrhizin can impede COVID-19 S-protein binding to ACE-II receptors. Emodin, a bioactive antiviral agent may hamper S-protein binding to ACE-II receptors (Preeti Pandeya, 2020). On that account Emodin and apparently Aloe-emodin can block the COVID-19 infection by engaging with S-protein in binding to ACE-II (Pius T. Mpiana, 2020). Based on this outlook, relevant compounds could be pertained in impediment and management of COVID-19 entirely or in amalgamation with traditional interventions (James M. Sanders, Marguerite L. Monogue, Tomasz Z. Jodlowski, & James B. Cutrell, 2020).

Natural Metabolites Inhibiting Activity of Coronavirus

The blooming of vaccines against coronaviruses countenances various challenges intrinsic to its establishment as safe, efficient, production and distribution. Essentially, the treatment is based on the control of symptoms and the repression of viral replication (COVID-19: towards controlling of a pandemic, Volume 395 2020). Additionally, curbness over this infection via social measures can limit the transmission (Renyi Zhanga, 2020). A concern in the development of any antiviral treatment, encompassing synthetic drugs, is the discernment with regard to the virus and not the host metabolism, specifically meaning, giving rise to efficacious treatment with low toxicity (Singhal, 2020). In this context, the pharmaceutical industry often turns to natural products with antiviral activity (Nadeem, 2020).

Various natural sources from biome have been evaluated with regard to anti-SARS-CoV-1 activity and utilized as a scaffold in drug development since its outburst in 2003. These natural metabolites comprise of terpenes, glycosides, tannins, fatty acids, alkaloids, flavonoids and phenylpropanoids (K. Chojnackaa, 2020). The diverse nature of these chemical classes is associated with distinct mechanism utilized by each phytochemical class which is effective enough to inhibit coronaviruses. Nonetheless, the chemical structures of these natural metabolites present conventional attributes that validate the interpretation of Jo et al. (2019), who via in silico analysis depicted those SARS-CoV-1 inhibition needs chemical structures containing a hydrophobic aromatic ring, hydroxyl groups and carbohydrate moieties. However, not all of these anti-SARS-CoV-1 compounds contain an aromatic ring; their molecular structures have lipophilic and hydrophilic rings and the potential to form miscellaneous hydrogen bonds through hydroxyl groups (Robabeh Baharfar, 2015).

Diverse anti-SARS-CoV-1 natural metabolites also have other bioactive properties against various viral infections and diseases. For exemplification, the marine sponge mycalamide A and its analogue mycalamide B, both display bioactivity against the Herpes virus. Temporarily, the flavanol myricetin show antiviral activity against leukemia, HIV and the influenza virus. Furthermore, lycorine is also well known for its broad medicament implementation depicting its anti-oxidant, anti-bacterial, anti-tumoral, anti-cancer and anti-inflammatory properties (Rajesh Ghosh, 2020).

Bioactive compounds including chloroquine phosphate and hydroxychloroquine reveal promising activities with possible inhibitory action so as to combat the effect of SARS-CoV-2 virus. It has been clearly elucidated in the illustration by Wen et al. (2007) that the natural metabolites including ferruginol, 8 ß-hydroxyabiet-9, 13-dien-12-one, 7 ß-hydroxydeoxycryptojaponol, 3ß, 12-diacetoxyabiet-6,8,11,13-tetraene, betunolic acid and savinin possessed IC50 values stretching from 0.63 (betunolic acid) to 1.57mM (3b,12-diacetoxyabiet-6,8,11,13-tetraene). Regardless of these values being extremely higher than the synthetic medications they constitute an exceptional bioactivity they represent a remarkable bioactivity within the natural products (Ashraf, 2020). As natural products comprising those metabolites were not concretely outlined to be used antagonist to coronaviruses but are frequently utilized and consumed by humans, their low IC50 values evinced the treatment of SARS-CoV-1 virus in an imperishable way. These medicaments can also prove to be efficacious against the prevelant SARS-CoV-2 virus. Additionally, the analysis of their molecular structures and biological mechanisms that aid in inhibition can render novel and innovative scaffolds for development of drugs (Sanjay Kumar Sonbhadra, 2020). These compounds include four abietane-type diterpenes, one triterpene and one lignan. Abietane-type diterpenes are metabolites that occur in conifer angiosperm species such as Araucariaceae, Cupressaceae, Phyllocladaceae, and Pinaceae and more specifically in families for instance Asteraceae, Celastraceae, hydrocharitaceae and Lamiaceae (Ananda da Silva Antonio, 2020). These diterpenoids have been isolated from a variety of terrestrial plant sources whereas the new abietane-type diterpenes have been isolated from Cryptomeria japonica. This class of metabolites exemplifies bioactivities encompassing antilucer, antitumor, anti-inflammatory, anti-diabetic, anti-microbial and anti-malarial and cardioprotection.

In these times the dominion of plant-based drugs is on the rise. But due to the existence of numerous compounds in crude extracts of plants it can prove to be either advantageous or show detrimental effects, depending upon the quantity that will be in use. These crude extracts are also

known to target individually at multitudinous sites in a virion particle; yet it is to be tested counter to SARS-CoV-2. These drugs that are derived from plants can affect the disruption of cell membrane functionally and structurally, intrusion of DNA/RNA synthesis and function, intervention in the normal cell communication just like quorum sensing in bacteria and the summoning of solidification of constituents of cytoplasm (K. Chojnackaa, Phytochemicals containing biologically active polyphenols as an effective agent against Covid-19-inducing coronavirus, 2020). Several key events in the pathogenic pathways are also affected by formulated plant-based products. For instance, curcumin is known to be efficacious for its anti-proliferative, anti-inflammatory, anti-angiogenic, anti-viral and anti-oxidant effects. It can also regulate redox position, transcription factors, protein kinases, adjuvant molecules and cytokines in the human body (Balachandar Vellingi, 2020). It has also been disseminated by in silico estimation that anti-SARS CoV plant-based drugs could be one of the most precious drug targets against SARS CoV-2. Thus plant metabolomics is bound to serve a prime role in the development of novel drugs and medications (Lovnish Thakur, COMBATING SARS-COV-19 BY PHYTOCHEMICALS: AN IN SILICO STUDY, 2020).

Repurposed Drugs Against Covid-19

In early March 2020, the antimalarial drugs hydroxychloroquine and chloroquine exhibited in vito and in vivo pursuit antagonist SARS-CoV-2 in small trivial geospecific trial sets. Hydroxychloroquine and chloroquine belong to the quinolona family and are known to be the synthetic derivatives of quinine-an alkaloid extract isolated from the bark of the Cinchona tree. Since the 17th century, cinchona bark was formerly used as an antifever drug and later as antimalarial drug. Although there lays a difference in the therapeutic and toxic doses of chloroquine and hydroxychloroquine, they are related drugs with indistinguishable clinical indications for use and analogous disclosure of retinal toxicity (Petter I. Andersen, 2020). The most popular quinolones are fluoroquinolones which include Ciprofloxacin (Cipro), lomefloxacin (Maxaquin), norfloxacin (Noroxin), ofloxacin (Floxin), moxifloxacin (Avelox) and levofloxacin (Levaquin). All of these can be ingested in the form of a pill whereas moxifloxacin and levofloxacin can be injected or implanted as well. Quinolones show antibacterial activity by inhibiting replication of bacterial DNA via blocking the ligase domain of bacterial DNA gyrase (topoisomerase II); some also inhibit topoisomerase IV. Although there are many accepted, repurposed drugs presently in clinical trials, but hydroxychloroquine (Plaquenil) and chloroquine are the two major drugs that have been in the headlines as budding drugs for treatment of COVID-19. Despite of the availability of these drugs the more potentiality has been discovered in bioengineered antibodies (developed using vector as a vehicle) and therapies relieing on cytokines and nucleic acid (DNA/RNA) which directly target the gene expression (protein formation) of a virus (Yi-Chi Wua, 2020). For instance, the repurposed drugs encompassing favipiravir, remdesivir (Donald C. Hall Jr., 2020), lopinavir, ritonavir, nebulized α-interferon, ribavirin and interferons have been illustrated to broadcast its efficacy as a treatment of the deadly virus SARS-CoV-2 (Yang Yang M. S., 2020). In addition to this peptide vaccine acting as a therapeutic medicine has also reached the process of clinical trial. Lately, plasma therapy has also shown favourable and propitious results so as to elevate the use of this method which can help get rid of this deadly virus from the society (Muhammad Adnan Shereen, 2020). Though these therapies and drugs give positive and encouraging results but we all are aware of the side –effects they are bound to give us indirectly, so scientists are still putting effort to discover some pre-eminent drug and multi-epitope vaccines against SARS-CoV-2 virus. Hence there emerges an urgent requirement for safe, cheap, efficacious drug or a therapy with trivial or insignificant side-effects for the treatment of COVID-19.

Bioactive Compounds Illustrating Antiviral Activity: Mechanism of Action and Structure

Polyphenols

Polyphenols are the naturally occurring compounds found in plants including phenolic acid and flavonoids that majorly benefit the human body to fight over infections and diseases (Rizvi, 2009). Primarily, polyphenols comprise of numerous phenolic rings and are categorized into phenols, flavonoids, lignans, hydroxycinnamic acid, coumarin, phenylpropanoids and hydroxybenzoic acid. (Giuseppe Annunziata, 2020)It has been illustrated in the former studies that the phytochemicals contained in the extract taken from S. nigra, outlined the existence of cyanidin, kaempferol, myricetin, dihydromyricetin, and quercetin derivatives 3-, 4-, and 5- caffeoylquinic acid; kaempferol 3-rutin; rutin; pelargonidin 3-glucoside; isorhamnetin 3-rutin, isorhamnetin 3-glucoside and flavonols (5,7,3´,4´ -tetra-O-methylquercetin and 5,7-dihydroxy-4-oxo-2-(3,4,5- trihydroxyphenyl)chroman-3-yl3,4,5-trihydroxycyclohexanecarboxylate). Therefore, it was also outlined that some of these polyphenols derived from S. nigra, portrayed antiviral activities. Thus, in this regard it can be hypothesized that the antiviral activity is endeavoured by the various classes of phytochemical compounds which in turn, are accountable for a synergistic effect. Additionally polyphenols have been discovered in diverse plants which exhibit antiviral activity against a broad stretch of viruses inclusive of HIV-1, HIV-2, HSV-1, HSV-2, Influenza virus, Dengue virus, HBV, HCV, Infectious bronchitis virus (IBV), Murbarg virus, Ebola virus, Newcastle disease virus

(NDV), Poliomyelitis-1 virus, Lentivirus, and Coronavirus. Polyphenols are known to work antagonist coronaviruses utilizing discrete mechanisms encompassing activating or inhibiting cellular signaling pathways or faltering papain-like protease (PL^{pro}) and 3-chymotripsin-like protease ($3CL^{pro}$) enzyme. Also few other polyphenolic compounds (30-(3-methylbut-2-enyl)-30, 4-hydroxyisolonchocarpin, broussochalcone A, 4,7-trihydroxyflavane, broussochalcone B, papyriflavonol A, kazinol A, kazinol B, kazinol F, kazinol J, and broussoflavan A) which have been secluded from Broussonetia papyrifera illustrate propitious activity against SARS CoV. The studies predict that exorbitant efficacy against PL_{pro} as perceived by these compounds via activity against M_{pro} or $3CL_{pro}$ does not reach upto the standard. In particular, papyriflavonol A preoccupies spectacular activity against SARS CoV. It has also been disseminated by in silico analysis that polyphenols have the characteristic to obstruct SARS CoV-2 Mpro and RdRp with great efficacy. In another major study, it was found that another broadly dispersed, low molecular weight phenolic compound entitled as a flavonoid which depicted strong antiviral activity against SARS CoV (Hashem, 2020), Influenza virus, HBV, HSV, HCV, HIV, Dengue virus, Simian virus, Human rotavirus, Bovine viral diarrhea virus, Poliomyelitis-1 virus, Vesicular stomatitis virus (VSV), and Newcastle disease virus (NDV). Flavonoid type compounds, including apigenin and quercetin, illustrated the activity against SARS CoV virus through the obstruction of M_{pro} enzymes with an IC_{50} of 38.4 ± 2.4 μM and 23.8 μM, individually. The prediction made through in silico analysis also states that compounds containing flavonoids can put an end to the activity of M_{pro} of SARS CoV-2.

Alkaloids

Alkaloids represent a structurally diverse category of nitrogen-containing basic compounds which are categorized into distinct groups based on their heterocyclic ring, like namely tropanes, pyrrolidines, isoquinoline purines, imidazoles, quinolizidines, indoles, piperidines, and pyrrolizidines. These classes of alkaloids are very much favourable against HIV-1, HSV-1, HSV-2, DNV, VSV, Influenza virus, and Newcastle disease virus (NDV). Diverse types of alkaloids exemplified anti-SARS activity encompassing hindrance emetine, Ipecac, Macetaxime, tylophorine, and 7-methoxy cryptopleurine, via the obstruction of protease enzyme, RNA synthesis, and protein synthesis. Additionally, few alkaloid compounds act against SARS CoV as a nucleic acid intercalating agent, for example; tetrandrine, fangchinoline, cepharanthine, and lycorine through disintegrating nucleic acids and creating a hindrance projection and nucleocapsid proteins (Onat Kadioglu, 2020). Virtual screening analysis disclosed that 10-Hydroxyusambarensine and Cryptoquindoline—the two alkaloid compounds secluded from African medicinal plants depicted anti-SARS CoV and anti-SARS CoV-2 activity via inhibition of their Mpro. It can be thereby concluded that certain plant-based drugs i.e. in the form of alkaloids can be considered as a substitute drug target for the treatment of COVID-19.

Saponins

Saponins are another class of naturally occurring glycosides with foaming characteristics. These are the phytochemicals which can be found in most of the vegetables, beans and herbs. The finest known sources of saponins include peas, soybeans and some herbs with foaming properties namely soapwort, soaproot, soapbark and soapberry. Saponins used extensively for commercial purposes are extracted chiefly from Yucca Schidigera and Quillaja saponaria. Recent studies have revealed the beneficial effects of saponin in maintaing blood cholestrol levels, cancer, bone health and acting as an immunity booster. They are broadly considered for stimulating the immune system in humans (Robabeh Baharfar, 2015). The plants release saponins to fight infections by parasitic organisms. When they are ingested by humans these saponins then play a major role in providing protection against viruses and bacteria (Ilkay Erdogan Orha, 2020). These ubiquitious known compounds extracted from plants are known to demonstrate antiviral activity against Newcastle disease virus (NDV), Simian (SA-11) virus, Murinenorovirus (MNV) and Feline calcivirus (FCV), RSV,VSV, HSV-1, HSV-2, HIV-1, Epstein-Barr virus (EBV) and human (HCR3) rotaviruses, Influenza virus and Dengue virus.

Terpenes

Terpenes constitute a large class of natural products built up from isoprene units. These isoprenoid compounds are classified based on the number of isoprene units present in the structure, namely monoterpenes, sesquiterpenes, diterpenes, triterpenes, tetraterpenes and polyterpenes. These terpenes illustrated antiviral activity counter to Bovine viral diarrhoea virus, HSV-1, Poliovirus type-2 (PV-2) and vesicular stomatitis virus (VSV), Dengue virus serotype-1 (DENV-1), Influenza A and B viruses, HIV-1 and HIV-2 and majorly SARS-CoV. The studies conducted formerly reveal that ten diterpenes, two sesquiterpenes and two triterpenes exhibit anti-SARS-CoV activity with IC50 ranging from 3-10 μM. Additionally the studies conducted via in silico experiments demonstrated that terpene namely Ginkgolide A can firmly block SARS-CoV-2 protease enzyme (Anuj Kumar, 2020).

Conclusion

The present-day COVID-19 pandemic is distinctly an international public health issue. In the face of this considerable global challenge, scientists all around the world are trying hard to come up with the most effective antiviral drug to combat SARS CoV-2. Bioactive compounds can layout an answer to this predicament, as they often show low toxicity. Due to the similarity between SARS-CoV-1 and SARS-CoV-2 there is a great hope that a vaccine can be produced as early as possible. The contemporary study deals with the possible anti-SARS-CoV-2 activity of polyphenolic compounds, alkaloids, terpenes, saponins etc which could help researchers ponder upon a new dimension. Therefore, due to expeditious transmission, countries around the globe must expand awareness into disease monitoring systems and scale-up nation's preparedness and retaliation operations together with setting up quick response squads and upgrading the capacity of the national laboratory system.

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