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REVIEW ARTICLES

Natural therapeutics against SARS CoV2: the potentiality and challenges

Anirban Bhar[1] · **Akansha Jain**[2] · **Sampa Das**[2]

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Abstract

The incidence of the COVID-19 pandemic completely reoriented global socio-economic parameters and human civilization have experienced the worst situation in the recent past. The rapid mutation rates in viruses have continuously been creating emerging variants of concerns (VOCs) which devastated different parts of the world with subsequent waves of infection. Although, series of antiviral drugs and vaccines were formulated but cent percent effectiveness of these drugs is still awaited. Many of these drugs have different side effects which necessitate proper trial before release. Plants are the storehouse of antimicrobial metabolites which have also long been utilized as traditional medicines against different viral infections. Although, proper mechanism of action of these traditional medicines are unknown, they may be a potential source of effective anti-COVID drug for future implications. Advanced bioinformatic applications have opened up a new arena in predicting these repurposed drugs as a potential COVID mitigator. The present review summarizes brief accounts of the corona virus with their possible entry mechanism. This study also tries to classify different possible anti COVID-19 plant-derived metabolites based on their probable mode of action. This review will surely provide useful information on repurposed drugs to combat COVID-19 in this critical situation.

Keywords Covid-19 · Natural medicine · Nutraceuticals · Plant metabolites · Therapeutics

Introduction

The covid-19 outbreak has completely destabilized rational human life for the past couple of years and made humanity experience its greatest challenge in the recent past. To date (as of 21st January 2022) more than 347 million confirmed cases of Covid-19 have been observed across the globe with 56 lakh deaths (https://covid19.who.int). The third wave of coronavirus outbreaks has gradually shoot up again with an average daily increase of 36 lakh cases has been encountered as of 0:00 GMT + 0 on 21st January 2022 (https://www.worldometers.info/coronavirus). With constant selection pressure and a high rate of mutability, SARS CoV2 are constantly changing their nature and devastated the world with the new potential of virulence (Huang et al. 2020). Although several vaccines have been developed against these corona viral strains but rapid emergence of new variants warns about the future inability of these vaccines against viral strains. Most of the newly emerging SARS CoV2 variants are capable to evade human immunogenic interactions as well can mask the function of neutralizing antibodies (NAbs) developed in response to vaccines (van Oosterhout et al. 2021). A multifaceted approach has been employed to combat such situations. For example, the development of plant-derived vaccines using engineered virus-like particles (VLPs) may prove to be a potent alternative in the future (Bhar 2021). Besides, many plant metabolites may provide excellent therapeutic alternatives towards Covid-19 treatment.

Plants are the repertoire of varied secondary metabolites and metabolic proteins which have enormous medicinal

✉ Anirban Bhar
anirbanbhar06@gmail.com; anirbanbhar@rkmvccrahara.ac.in

✉ Sampa Das
sampa@jcbose.ac.in

Akansha Jain
akansha007@rediffmail.com

[1] Post Graduate Department of Botany, Ramakrishna Mission Vivekananda Centenary College, Rahara, Kolkata 700118, India

[2] Division of Plant Biology, Bose Institute, Centenary Campus, P 1/12, CIT Scheme, VII-M, Kolkata, West Bengal 700054, India

values. Although the actual mode of action of most of these chemicals is still unknown, screening of some effective plant metabolites and detailed analyses will generate treasures of effective natural medicines in the future. Although out of the purview of this present review, many interesting receptor kinase inhibitors have already been reported from plants to inhibit spread of cancerous tissues (Paul et al. 2021). Natural medicines derived from plant products are mostly non-toxic, well-tolerated with minimum side effects, and highly absorptive in nature by the immunogenic pathways of the human body. Polyherbal formulations along with hydrotherapy particularly practiced in Nigeria had proved to be effective in symptomatic relives of pneumonic patients (Lawal and Omogbene 2021). Application of these natural drugs along with the conventional treatment may help to minimize the death rates as well as infection rates in the future. The present review briefly summarizes the types of coronaviruses and their basic mechanism of entry inside the host body. The effect of different plant-derived medicinal compounds against Covid-19 has been discussed along with their targets against SARS CoV2. This review will surely provide an insight into the different plant-derived metabolites for their potential use against Covid-19 in the future.

Coronavirus family associated with the pathogenesis

Coronaviruses are riboviria, as contains RNA as genetic material. These viruses belong to the family Coronaviridae, which in turn falls under the hierarchical lineage of Coronavirineae and order, Nidovirales. Coronaviridae family is further classified into two subfamilies, Letovirinae and Orthocoronavirinae. Letovirinae contains a single clade of viruses called α letovirus whereas Orthocoronavirinae contains four clades, α coronavirus, β coronavirus, δ coronavirus, and γ coronavirus (Helmy et al. 2020). Among these four, α coronavirus and β coronavirus had the bat and rodent lineage. On the other hand, δ coronavirus and γ coronavirus belonged to avian lineage (Fig. 1). Most of the human pathogenic forms are reported from α and β clades. HCoV-OC43, HCoV-229E, and HCoV-NL-63 are all α coronaviruses and are responsible for the common cold, self-limiting upper respiratory tract infection in immune-compromised patients. On the contrary, human pathogenic forms reported from β coronaviral origin e.g., SARS CoV (Severe Acute Respiratory Syndrome Corona Virus), SARS CoV-2, and MERS CoV (Middle East Respiratory Syndrome Corona Virus) are responsible for severe respiratory disorders with extreme manifestation and high mortality (Li 2016).

The basic mechanism of entry

The primary receptor for SARS CoV2 is human angiotensin-converting enzyme 2 (ACE 2) which is displayed in cell surfaces. The spike (S) protein of SARS CoV 2 interacts with ACE 2 by the receptor-binding domain (RBD) located in the S1 domain. S2 domain help in the internalization of the attached viral particle. In this whole process host proteases, TMPRSS 2 and Furin plays a huge role. Furin cleaves at the S1/S2 cleavage site that opens up the RBD and promote the RBD-ACE 2 interaction. On the other hand, TMPRSS 2 helps in the successful interaction and membrane fusion of

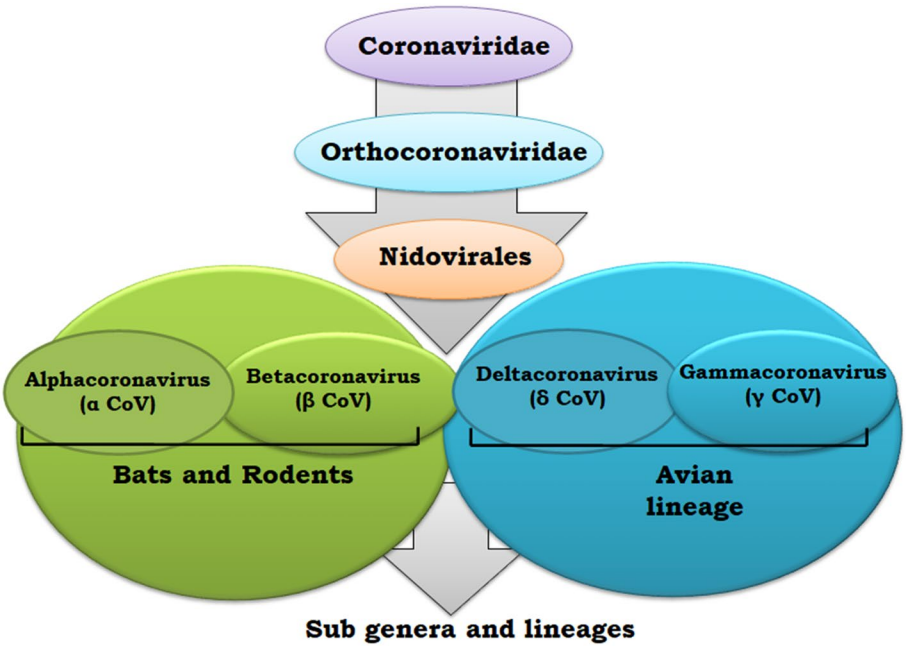

Fig. 1 Schematic representation of major classification of corona virus

viral glycoprotein with the host cell membrane (Luan et al. 2020). Besides, many other potential receptors popped up recently delineating their possible role in viral entry. Neuropilins are the transmembrane glycoproteins mainly located in the growing neurons which help in neuron development. Neuropilin 1 (NRP1) and neuropilin 2 (NRP2) are the receptors of class III semaphorin receptors and are also targeted by several ligands responsible for angiogenesis (Lin et al. 2021). Neuropathological analysis with Covid-19 autopsies has revealed that cleaved S protein interacts with NRP1 and NRP2, which in-turn help the virus to infect the nervous system of the human being (Daly et al. 2020; Cantuti-Castelvetri et al. 2020). Another immunoglobulin family protein CD147 also known as *basigin* or EMMPRIN is a transmembrane glycoprotein that has now been identified as an alternative facilitator of SARS CoV2 entry inside the host cell. Anti CD147 antibody was found to readily block SARS CoV2 entry (Wang et al. 2020a, b). Another interesting finding demonstrated that α-keto acid sugars may take a key part in the entry of SARS CoV2 as well as subsequent "cytokine storm" (Hatmal et al. 2020; Wielgat et al. 2020). Detailed analysis with all these receptor proteins may provide further clues to solve puzzles in SARS CoV 2 entry and develop new strategies to combat this disease (Fig. 2).

Plants are the repertoire of unknown wonder drugs

Plants harbor a variety of molecules with ethnomedicinal properties. Although the detailed mode of action of these drugs is still unknown, based on preliminary published data and computational screening approaches natural therapeutics can broadly be classified and described into following sections (Table 1),

DNA/RNA intercalation, prevention of viral replication, and inhibition of virus

Alkaloids are diverse chemical compounds mainly characterized by heterocyclic nitrogen compounds and are alkali by nature. This wide group of compounds is mostly produced by the plant species but recently different microbes along with some marine organisms have also been reported to produce many alkaloids (Zotchev 2013). Plants are the largest producer of alkaloids as secondary metabolites (e.g., morphine, strychnine, quinine, ephedrine, nicotine). Many of these alkaloids have potential drug activity (Peng et al. 2019). They have a very wide range of mechanisms in modulating diseases (Matsuura and Fett-Neto 2015). Many plant-derived alkaloids have shown intercalation activity against nucleic acids (DNA or RNA). The most popular nucleic acid intercalation alkaloids are berberine, emetine, sanguinarine, isoquinoline, beta-carboline. Alkaloids quinoline, paraquinine, dictamine, skimmianine also act as intercalation

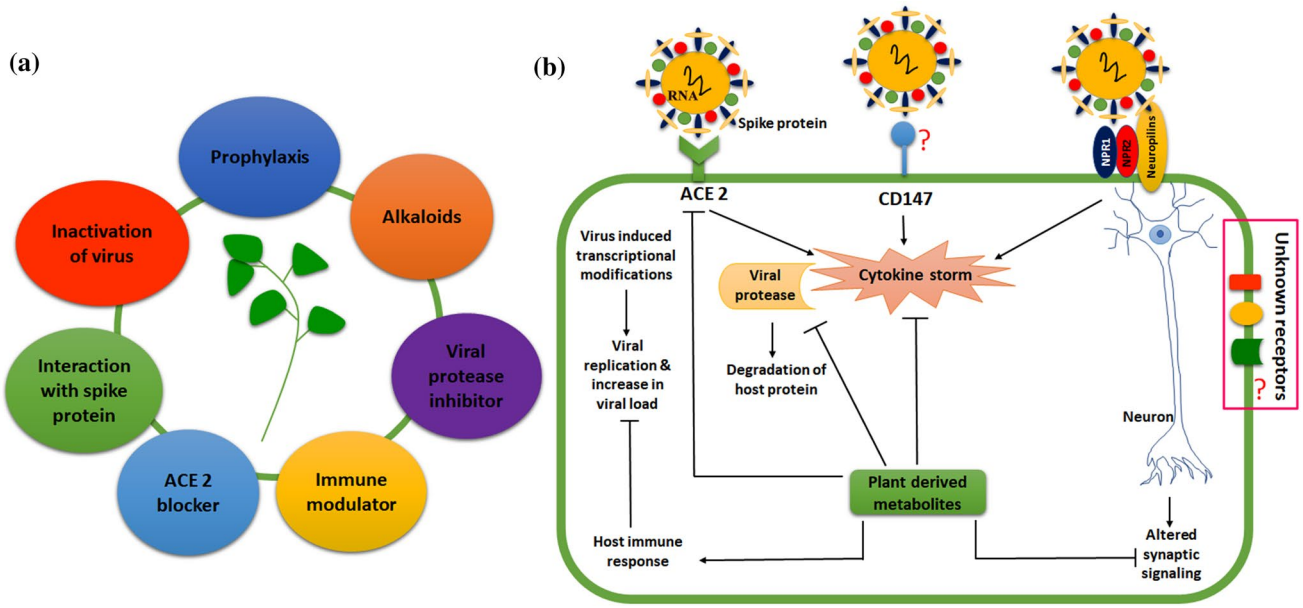

Fig. 2 Natural therapeutic drugs; **a** diagrammatic representation of different major classes of natural medicines against SARS CoV2; **b** representation of mechanism of entry of SARS CoV2 within host cells and the probable inhibition mechanism of PDMs (plant derived metabolites)

Table 1 List of different classes of natural therapeutic agents against SARS CoV2 based on their probable mode of action

Proposed classes of natural therapeutics	Basis of classification	Principal compounds	Probable modes of action	References
Class I	Nucleic acid intercalating agents	Morphine, strychnine, quinine, ephedrine, nicotine, berberine, emetine, sanguinarine, isoquinoline, beta-carboline, quinoline, paraquinine, dictamine, skimmianine, hydroxyquinoline, Beta carboline, Atropine, gallic acids, Crabescidin etc.	DNA/ RNA intercalation, prevention of viral replication and inhibition of virus	Peng et al.(2019), Wink (2020), Sinha and Balayla (2020), Andrade et al. (2020), El-Demerdash et al. (2021)
Class II	Protease inhibiting agents	Carvacrol, compounds from *Aloe vera* and *Andrographis paniculate* etc.	Inhibition of virus specific protease, M^{Pro}, $3CL^{pro}$ etc.	Javed et al. (2020), Mpiana et al. (2020), Enmozhi et al. (2021)
Class III	Immune modulators	Ginsenoside Rg3, resveratrol, batatasin I, allicin, quercetin. Extracts from *Humulus lupulus*, *Cinnamum verum* etc.	Inhibit NF-κβ and pro-inflammatory	Lucas et al. (2021), Alhazmi et al. (2021)
Class IV	ACE 2 blockers	Flavonoids, xanthones, proanthocyanidins, secoiridoids, citric acid, rutin, quercetin-3-O-glucoside, tamarixetin, and 3,4-dihydroxyphenylacetic acid, citronellol, geraniol, neryl acetate, limonene etc.	Interfering viral entry, destabilizing Spike protein-ACE2 interaction.	Muchtaridi et al. (2020), Ghoran et al. (2021), Liu et al. (2020), Senthil Kumar et al. (2020)
Class V	Virus inactivation agent	*Maackia amurensis* seed lectin (MASL) etc.	Interaction with viral spike glycoprotein e.g., MASL interacts with this sialic acid present in spike protein.	Sheehan et al. (2021)
Class VI	Prophylactic agents	Catechins, epigallocatechin, curcumin. Extracts of licorice, ginger and tulsi etc.	–	Xu et al. (2017), Henss et al. (2021), Manoharan et al. (2020), Jain (2021)

alkaloids. These intercalation alkaloids directly interact with DNA or RNA and hence stabilize those in single-stranded form. These conjugates (DNA alkaloids or RNA alkaloids) readily inhibit their further replication. This machinery is adopted to inhibit SARS CoV 2 by plant-derived alkaloids (Wink 2020). It has been noticed that partially hydroxyquinoline has shown activity against covid-19 disease (Sinha and Balayla 2020). This led the scientist to test and survey other alkaloids against these deadly viruses. Beta carboline is very effective against SARS CoV-2 based on in silico screening (Andrade et al. 2020). Atropine and gallic acids were previously found to be effective against DNA viruses (harpies simplex Type 1) and RNA viruses (parainfluenza type 3) (Özçelik et al. 2011). Another intercalating alkaloid berberine was reported to be active against an array of viruses e.g., human cytomegalovirus (HCMV), herpes simplex virus (HSV), human papillomavirus (HPV), and also human immunodeficiency virus (HIV). In all these cases, the above alkaloids interact with replication machinery by inhibiting different stages of the life cycle (Warowicka et al. 2020). Emetine and ipecac group of alkali have long been used as anti-amoebic drugs and can also be effective against SARS CoV-2. Emetine had already shown its high effectivity (EC_{50}) against MERS (Middle East respiratory syndrome) and SARS (severe acute respiratory syndrome) (Bleasel and Peterson 2020). Guanidine alkaloids produced by marine organisms are well known for their antiviral activities. A detailed in silico screening was performed against essential coronavirus proteins, for example SARS CoV-2 main protease (MPro), spike glycoprotein (S protein), membrane glycoprotein, nucleocapsid phosphoprotein, and non-structural protein 10 (nsp10). Crabescidin 786 and 826 exhibited binding activity and can act as potential anti-covid-19 agents (El-Demerdash et al. 2021). Many other alkalis used as cocktails in A-E obtained from *Melicopetelifolia* showed effectiveness against the influenza virus. Tomatidine steroidal alkaloid isolated from young and ripe green tomato plants exhibited innovatory effects against Chikungunya virus (CHN), as well as flaviviruses like dengue virus (DENV) and zika virus (ZIKV) (Troost et al. 2020). The screening of these antiviral alkaloids against SARS CoV-2 may provide more insight into their mechanism of action and efficacy in the future.

Viral protease inhibitor

The major drawback of the development of antiviral drugs is the absence of independent molecular machinery. Recently, determination of SARS CoV-2 proteases provides new hope for the development of antiviral drugs by targeting M^{Pro} (Ullrich and Nitsche 2020). Viral M^{Pro} is completely different from human proteases, that is why targeting SARS CoV-2 protease by any drugs will not functionally inhibit human proteases. Carvacrol a monoterpenoid phenol abundantly present in aromatic plants, for example, oregano, thyme was effective against SARS CoV-2 by inhibiting M^{Pro} (Javed et al. 2020). Accelerated free energy perturbation-based absolute binding free energy prediction has shown 15 repurposed drugs interacting with high efficiency. Among them, chloroquine compounds were also showed a high binding rate (Li et al. 2020), but these should be cross verified through proper wet-lab experiments. Virtual study and docking experiments have also been extensively done to screen a wide variety of plant chemicals effective against M^{Pro}. Mpiana et al. (2020) have identified three active ligands from *Aloe vera* that can inhibit SARS CoV-2 protease (3CL pro) which is responsible for replication of the virus and the compound isolated from *Andrographis paniculata* also showed potential inhibitory effect against SARS CoV-2 M^{Pro} (Enmozhi et al. 2021). The inhibition of replication of virus particles is the key inhibitory pathway. The phytochemicals from *Houttuynia cordata* Thunb. were reported to inhibit Main protease (M^{pro}), Papain-Like protease (PL^{pro}) and ADP ribose phosphatase (ADRP) which are the principal enzymes involved in viral replication (Das et al. 2022). In silico screening and binding energy analysis have revealed that phytochemicals from many traditional antiviral plants (neem, tulsi and turmeric) can also efficiently inhibit viral replication by deactivating the above-mentioned enzymes. The polyphenols from tea, (−)-epicatechin-3-O-gallate (ECG) was shown to be efficient binding partners with M^{Pro} and PL^{Pro} (Gogoi et al. 2021).

Plant metabolites as immune modulators

The specific drug against Covid-19 is still elusive. The only option to date is supportive therapeutic approaches. In such a situation, immunomodulators have a positive effect on this disease. The nonspecific inflammation of different organs such as liver, kidney including neurological and cardiovascular complications are prominent due to massive "cytokine storm" (Wang et al. 2020a, b). An initial study with alcoholic extract of hop (*Humulus lupulus*) and bark of cinnamons (*Cinnamum verum*) has shown some positive immunomodulation effects. Alcoholic extract from these plants was found to inhibit NF-κβ (nuclear factor kappa-light-chain-enhancer of activated B cell) which acts as a pro-inflammatory element (Lucas et al. 2021). The effect of different plant-derived compounds ginsenoside Rg_3 from *Panax quinquefolius*; resveratrol from *Vitis vinifera*; batatasin I from *Dioscorea batalas*; shikonin from *Lithospermum erythrorhizon*; diallyl thiosulphinate (allicin) from *Allium sativum*; and quercetin from *Moringa oleifera* were extensively reviewed by Alhazmi et al. (2021).

The potential ACE 2 blockers

ACE 2 is trivial for the entry of SARS CoV-2 into human cells. As discussed earlier, spike proteins directly interact with ACE 2 for the successful entry of the virus and pathogen. Hence, the simplest way to prevent corona viral infection is by blocking its principal receptor ACE 2. Several plants derived metabolites have shown their binding affinities towards ACE 2, hence, extends their possibility for a potential drug against Covid-19. Flavonoids, xanthones, proanthocyanidins, secoiridoids. have potential natural therapeutic activity against SARS CoV-2 by blocking ACE 2 (Muchtaridi et al. 2020).

Vitamin C (citric acid) has a prominent role in scavenging oxidative damage due to ACE 2–S-protein interaction. The inhibitory function of flavonoids isolated from *Citrus* plants (naringenin, hesperidin, neo-hesperidin, nobiletin) along with the high concentration of Vit C was found promising against human ACE 2. These compounds were found to reduce inflammation, oxidative damage and viral load efficiently (Ghoran et al. 2021). Polyphenol compounds with B ring 3′,4′-hydroxylation (rutin, quercetin-3-O-glucoside, tamarixetin, and 3,4-dihydroxyphenylacetic acid) were tested against recombinant human ACE 2 receptor and among this quercetin was found to inhibit ACE 2 more efficiently as determined by fluorescence determination (IC_{50} = 4.48 µM) (Liu et al. 2020). Many non-specific studies using crude extracts from different plants were also taken forward to find out probable anti-Covid-19 compounds. Pomegranate peel extract showed antiviral activity by destabilizing glycoprotein and viral protease as well as ACE 2 destabilizing effect in an in vitro study (Tito et al. 2021). Essential oils isolated from lemon and *Geranium* have significantly downregulated the expression of human ACE 2 receptors in epithelial cells. Gas chromatography-mass spectrometry (GC–MS) based detection was performed and citronellol, geraniol, and neryl acetate from geranium oil and limonene detected from lemon oil were identified as key compounds in hindering ACE 2 activity (Senthil Kumar et al. 2020). More intriguing analyses are necessary to select out an efficient antagonist of the ACE 2 enzyme.

Interaction with viral spike glycoprotein and inactivation of virus

The surface spike glycoprotein (S protein) is the most essential viral protein for successful entry inside the host cell described to date. S protein has two subunits, S1 bearing a receptor-binding domain (RBD) interacting with ACE 2 receptor and S2 which helps in viral entry through membrane fusion by six helical bundle formations with two heptads repeat domain (Huang et al. 2020). Most of the work carried out to decipher the role of natural plant-derived compounds in destabilizing spike glycoprotein is restricted as virtual docking experiments (Azim et al. 2020; Parvez et al. 2020; Puttaswamy et al. 2020). The efficacy of different synthetic, as well as natural compounds, were tested in silico for potential anti-spike glycoprotein activity. In many cases, natural compounds proved to be better respondents than synthetic compounds (Jomhori and Mosaddeghi 2021; Tallei et al. 2020). Lectins are the carbohydrate-binding proteins present predominantly in many parts of plants, fruits, and vegetables. These lectins particularly mannose-binding lectins have been reported to be potent antiviral proteins (Keyaerts et al. 2007). Recently, it has been reported that *Maackia amurensis* seed lectin (MASL) inhibits SARS CoV 2 by interacting with spike glycoprotein and ACE 2 receptor proteins (Sheehan et al. 2021). Spike protein and ACE 2 enzymes are highly glycosylated with sialic acid residues. MASL interacts with this sialic acid and suppresses the viral entry inside the host cell. Less toxicity, better bioavailability, and good absorption properties make plant-derived metabolites a competitive alternative. Extensive wet-lab experiments are needed to further confirm their potential application.

Plant metabolites as prophylactic agents

The term "prophylaxis" means medications or actions taken to prevent disease. This is very much similar to modulations of immune responses or supportive nutritional therapy to prevent any kind of primary as well as secondary infections. Natural plant derived metabolites are widely used as a prophylactic agent against Covid-19. Due to extensive health risks, most works in this field had been performed virtually. The advent of the latest computerized techniques permits screening of many natural compounds to test their efficacy as medical probiotics. *Juniperus communis*, *Thymus vulgaris*, *Curcuma longa*, *Rosmarinus officinalis*, *Ocimum basilicum*, *Melissa officinalis*, and *Mentha piperita* were found to be very effective crude antiviral agents (Sampangi-Ramaiah et al. 2020). Besides, *Allium cepa*, *Malus domestica*, *Fagopyrum esculentum* were also reported to inhibit viral replication (Zhang et al. 2020; Lee et al. 2015). Green tea (*Camellia sinensis*) due to the presence of an excessive amount of catechins has long been known as an antioxidant, anti-inflammatory, anti-infection as well as broad anti-viral agent (Xu et al. 2017). Recently, it has been found that epigallocatechin predominantly presents in green tea successfully inhibits SARS CoV 2 infection (Henss et al. 2021). Another natural wonder compound curcumin extracted from *Curcuma* showed an attenuation effect against Covid-19 by activating pro-inflammatory angiotensin II-AT1 receptor signaling pathways (Manoharan et al. 2020). A computerized modeling-based study showed curcumin may act as an immunomodulator by reducing "cytokine storm" in affected

patients (Noor et al. 2021). The prophylactic nutraceutical activity of curcumin was also inhibits virus as well as reduces viral-induced pneumonia in affected patients (Thimmulappa et al. 2021). Another interesting finding showed that curcumin-based nanoformulations dramatically reduced post covid fibrosis by interacting with transforming growth factor β (TGFβ) mediated profibrotic pathways (Yo et al. 2021). Nutritionists also recommended *Glycyrrhiza radix* (licorice), *Zingiber officinalis* (ginger), *Ocimum sanctum* (tulsi) as immuneomodulatory drugs during the Covid-19 pandemic (Jain 2021). The traditional immunomodulator tulsi contains huge resources of flavonoids and essential oils which have a diverse effect on health modulations and anti-infectious properties. The major constituent in the *Ocimum sanctum* is eugenol (≥ 70%), methyl chavicol and essential oils, β caryophyllene, and carvacrol; which exhibited inhibitory roles on SARS CoV 2 (Maurya and Sangwan 2020).

Constraints of the utilization of natural therapy

Natural therapeutics has a long history to treat respiratory infections and many herbal drugs, along with nutritional additives are approved as drugs. For a natural therapeutic drug to be of excellence, it should be well-characterized, clinically tried and approved. Herbal drugs alone can neither get a patient rid of COVID-19 or other coronaviruses—nor can avoid the virus ingression but may relieve symptoms and potentially improve the general wellbeing of patients. Natural products are usually considered safe to use but in reality, all drugs carry risks (Ekor 2014).

The first and utmost important challenge is safety. It needs a meticulous reckoning of whether such herbal therapies are justified or not. Then again, its usage depends only if the disease is mild. Additional data is needed through restrained clinical trials to assist the efficiency of these natural drugs. Regulated trials to test efficacy and safety require constringent methodology, which may be lengthy and time-consuming (Yang 2020). Traditional application and belief do not affirm the suitability of herbs. Also, the mechanisms of action of herbal drugs are ambiguous. In fact, for many herbal drugs, the compositions of the concoction itself are unknown. Natural therapeutics are inadequately monitored as registered drugs in few countries making them easily available for purchase. This allows patients with COVID-19 to self-medicate and skip treatment at the hospital. It may be a cause to fear for patients with severe symptoms and may also disturb the Government's input in managing the disease. Though herbal drugs have so many constraints, it is undeniable that natural medicine can support the health of susceptible and old age patients or can at least slow down the transmission of the virus.

Conclusive remarks and future outlook

The recurrent occurrence of the COVID-19 pandemic hampers social behavior and imposes massive pressure on the healthcare system globally. Excessive infection rate develops a series of infected cases in a periodic fashion. The scientific community relentlessly tries to counter the infection spreads. Although, some vaccines were developed to contain the disease, in most cases they protect the infection to a certain percentage. Complete inactiveness of the infection is still intangible. Several antiviral drugs have been screened to study their effectiveness but this process needs several steps for final recognition of the drug. Plants are the proliferous source of different metabolites which have tremendous antimicrobial properties. Many plant-based medicines are used traditionally to cure different viral infections but the proper systematic study of those materials is lacking. In such a situation, a multifaceted approach should be taken to find out a possible way out. Natural medicines would be safe, as most of these plant-based medicines have a long ethno-pharmaceutical history and hence has comparatively less chance of cross-reactivity. Although the COVID-19 pandemic has led several researchers to screen plant-based products to use as repurposed drugs against SARS CoV2, a more organized approach is needed to the sustainable application of the same. At the present situation, natural medicines have wide opportunities but many important steps are to be addressed before that,

1. The organized repository of natural medicinal plants needs to be constructed.
2. Screening of the plants and detailed metabolic profiling of potent plants is an urgent requirement.
3. Development of natural medicine metabolite library has to be created.
4. More centralized approach has to be taken to find out potential compounds from huge metabolite libraries.
5. Categorization of metabolites based on their probable mechanism of action is needed.
6. Final experiments have to be pursued to prove the proposed mode of drug action.

Although the development of state of art natural medicine needs many further standardizations, still this is an urgent need for any future healthcare emergencies to mankind (Lawal et al. 2020).

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Declarations

Conflict of interest Authors declare there is no conflict of interest.

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