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Natural products as environmentally safe and green approach to combat Covid-19

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ARTICLE INFO

Keywords:  
Covid-19  
SARS-CoV-2  
Economic impacts  
Green chemistry  
Natural medicine

ABSTRACT

The Covid-19 pandemic is a major catastrophe in recent times that has taken a toll over the global scale in terms of the casualties, economic impact, and human beings' lifestyle. Scientists and researchers worldwide are dedicated to counter this issue using large-scale drug discovery and analysis to explore both the vaccination and the cure for Covid-19. However, almost all of the tested medicinal options cover allopathic medicines. A major issue associated with the above approach is the side effects that present a lacuna in arriving at an agreeable solution. To date, a total of >160,000,000 Covid-19 cases have been reported. However, to date, there is no report available on the scope and application of natural medicines in the treatment of the Covid-19. This review aims to target this area while covering the economic and other impacts of the Covid-19 on human life, the significance of greener solutions in counterdrug development, and the possible solutions of the Covid-19 using herbal drug treatment.

1. Introduction

The Covid-19 pandemic has considerably affected nations all across the world. Within the span of a year and a half, this issue has drawn the attention of worldwide scientists and researchers to explore and achieve the possible solutions in the course of both prevention as well as a cure [1,2]. Accordingly, the research in this area has been devoted to finding a suitable vaccination and arriving at a cure for this disease. Conventionally for viral infections, chemical medicines have been the most sought-after strategy [3]. However, the usage of the conventional synthetic organic compound-based allopathic medicines for treatment has come under some criticism in the past few years—the primary reason being the numerous side effects of such medicines. To counter the side effects of the allopathic medicines, it is often prescribed by the physician to consume multiple drugs. The overall influence on the human body becomes complex. Another issue is that the prolonged usage of the allopathic medicines renders the human body to develop immunity against these drugs, requiring stronger doses of these medicines that are not considered healthy to the body [4–6].

Over the years, it has been observed that the chemical extracts from natural products or so-called herbal medicines have been found to be effective against a number of diseases. This ranges from antimicrobial, antifungal, antimalarial, antiviral, anticancer, anti-HIV, etc. [7,8]. A major reason why the chemical medicines have been the most sought after is their quick action against the targeted disease. On the other hand, herbal drugs have been criticized for their comparatively slower action on the human body. However, a significant plus point associated with herbal medicines is their benign nature, which is significantly less likely to affect humans in any negative manner.

In the past few months, several articles have come across the literature describing the possible strategy to counter the Covid-19 pandemic [9–14]. However, all of them describe the treatment of the pandemic or potential vaccine using chemical medicines. To date, there is no research available in the literature on the application of herbal medicines in the treatment or possible vaccines for the Covid-19. The present article summarizes the chemical medicines and vaccines that have been proposed to counter the Covid-19. Some of the economic impacts of the Covid-19 have also been covered, and the overall impact of the Covid-19 on the life of human beings worldwide has been analyzed. Some of the green approaches for drug development have been discussed. A review of literature is presented on the use of herbal medicines that have been used to counter infectious diseases. It is postulated that in addition to the currently being investigated allopathic drugs and vaccines, herbal medicines could also be a possible solution to the pandemic.

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https://doi.org/10.1016/j.crgsc.2021.100114
Received 4 April 2021; Received in revised form 15 May 2021; Accepted 16 May 2021
Available online 21 May 2021
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2. A brief overview of the Covid-19

2.1. An introduction to the coronavirus

Human beings generally face a lot of pathological infections. In this context, the common pathogenic organisms of infectious diseases are primarily viruses [15], the latest being the Covid-19 [1,2]. There are almost 10,000 types of viruses known, although only a few are well recognized. Several commonly occurring viruses cause respiratory infections, including the influenza-related virus, human metapneumovirus, enterovirus, measles virus, herpes simplex virus, coronavirus, adenovirus, cytomegalovirus, etc. [16]. Since the onset of avian influenza, many viral infections have been reported in recent years [17]. The coronavirus was not usually widely recognized due to its weak affiliations with human beings. However, after the widespread SARS, the coronavirus received significant recognition. The bats have been reported to be one of the most common hosts of the coronavirus and were also the cause of the SARS and the MERS (Middle East respiratory syndrome) [18,19]. Including the SARS-CoV-2, there are around seven known kinds of the known coronaviruses that are contagious. Human coronavirus 229E, human coronavirus OC43, and human coronavirus NL63 are the commonly occurring coronaviruses that cause the cold to humans, although with considerably greater serious effects compared to the common cold [20]. However, it has now been recognized that the SARS and the Covid-19 have a serious influence on the human society. The WHO named the present virus the SARS-CoV-2, and it has a diameter of around 60 to 140 nm.

2.2. Covid-19 infection and the pandemic

The coronavirus disease-2019 (Covid-19) is caused by severe acute respiratory syndrome (SARS)-COV-2 virus (Fig. 1) [21,22]. It has been reported to have originated from Wuhan city of China, which is the capital of the Hubei province [23]. The SARS-CoV-2 is an enveloped RNA virus. Currently, it has been recognized that the Covid-19 mainly transfers from one patient to another human being [24,25]. There are mainly two modes of transmission that have been identified, (i) respiratory droplet transmission and the (ii) close contact transmission. With a single sneeze of human beings, around 40,000 saliva droplets erupt, and approximately 30,000 droplets come out with the coughing. Each of these saliva droplets contains almost 20,000,000 (20 lakh) of the coronaviruses, which then can float in the air along with the dust particles. This way, the coronavirus becomes airborne and enters the human body through the nose and mouth when the humans intake the virus-containing air or through other body parts depending upon the contact of the body with the surfaces having the adsorbed coronavirus. Therefore, the virus gains entry to the human body and primarily causes the infection to the lungs. Our lung cells contain the ACE2 Receptors (Fig. 2), and the spikes of coronavirus have a better capacity of binding with these receptors. This process of the entry of the virus inside the lung cells is known as endocytosis. Thereafter the virus becomes uncoated, and its RNA becomes free for replication. The entry of the coronavirus through the ACE2 receptors results in the highjack of the cell function by which it can form numerous new viruses. By replication, transcription, and translation, new viruses assemble and are released by exocytosis. The virus causes damage to the DNA of the host cell and causes the release of toxic molecules (Fig. 3), which affects the immune system. A possible mechanism of virus infection to the brain and the nerve cells is shown in Fig. 4. On the global level, vaccinations have started, and many people have received the vaccines. However, till May 10, 2021, there are a total of >160,000,000 Covid-19 cases reported worldwide. The total number of deaths that have been reported is >3,300,000, and a total of >140,000,000 people have recovered so far. A large number of cases and casualties were reported last year in Europe and the USA. USA, India, Brazil, France, Turkey, Russia, UK, Italy, Spain, and Germany have shown the highest number of cases. To date, the highest number of cases (>33,000,000) and the highest number of deaths (>599,000) have been reported in the USA. Currently, India is facing the second wave of Covid-19, and nearly 350,000 new cases are being reported daily, whereas close to 4000 deaths are taking place each day.

2.3. Economic impact of Covid-19

The first and foremost influence of the Covid-19 pandemic worldwide is on the stock markets, especially on Feb 24, 2020. Almost all of the major economies have received a crushing downfall due to the pandemic [26]. In addition, the growth rate of the GDP has suffered considerably [27]. There has been economic, social, and political instability and unrest in these times worldwide. An acute shortage of food worldwide, and a spike in the price of the goods, market disruptions has occurred. The education sector has suffered a great deal due to the outbreak of the Covid-19 pandemic [28]. Another significant influence of the pandemic has been the cancellation/postponement of international gatherings such as global conferences, sporting events, fashion extravaganzas, etc. The cinema halls have received closures, and so do the great and big business shopping malls, and the entertainment industry overall has received a setback. There has also been a disruption in the area of agriculture. The timely harvest of crops and the proper distribution of the food to the markets has not been functional on a regular basis due to the government rules on lockdowns and social distancing. The transportation industry related to aviation, cruise liners, train, bus, etc. sectors has also been practically stopped from work. The tourism sector, restaurant sector, gambling, and betting, etc., areas have also received drastic falls. There has been a global surge in unemployment due to the continuous periods of lockdowns. On the international level, there has been the closure of business and the loss of production and distribution.

3. Current investigated drugs and vaccines and their activity against the Covid-19

3.1. Drugs for the treatment of Covid-19

The coronavirus modifies its strain continuously, and therefore, there are no hundred percent effective drugs and active vaccines known until now. Some antibiotics, antiviral, plasma, and other medical treatments are currently in practice to treat the Covid-19 (Fig. 5). Antibodies function by locking the spike of virus and inhibiting their entry. The convalescent plasma also works in the same way. The drug chloroquine [14, 29], hydroxychloroquine [13,30], and Umifenovir [31] inhibit the uncoating of the virus. The drug hydroxychloroquine gained special attention during the pandemic. There was strong scientific evidence supporting the utility of this drug in the control of the Covid-19, while its...
usage was not approved by the FDA. Although even after a substantial initial promise, the WHO announced the stopping of the drug trials. Lopinavir, Ritonavir [32,33], Remdesivir [34], Darunavir [12], Ribavirin [35], Favipiravir [11], and Glycyrrhizin [9] inhibit virus replication. The Glycyrrhizin also inhibits toxic molecules. Disulfiram [36] inhibits the release of toxic molecules. Oseltamivir [37] inhibits neuraminidase enzyme, which inhibits exocytosis. A list of some of the drugs that have been evaluated against Covid-19 is shown in Table 1.

Fig. 2. Entry through ACE2 Receptors in lungs [122].

Fig. 3. Replication of virus in cell and toxic molecule release [122].
Fig. 4. Viral infection in brain and nerve cells [122].

Fig. 5. Possible Treatment of COVID-19 by targeting viral replication stages [122].
### Table 1
Some of the drugs that have been tested against Covid-19.

| Structure and name of drug | Remarks |
|----------------------------|---------|
| Chloroquine                | It is old antimalarial drug, recently reported as a potential antiviral drug. It has antiviral action against SARS-COV-2. Inhibit entry and uncoating of virus. Side effects: blurred vision, nausea, vomiting, diarrhea, headache |
| Hydroxychloroquine         | Antimalarial drug has similar antiviral action against SARS-COV-2. It is less hazardous than chloroquine. It inhibits entry and uncoating of virus. |
| Umifenovir                 | It is also known as Arbidol and may have potential to treat COVID-19. Arbidol impedes trimerization of SARS-CoV-2 spike glycoprotein. It inhibits entry and uncoating of virus |
| Lopinavir                  | Lopinavir is antiviral; drug Mechanism: acting as viral protease inhibitor, currently used against HIV. It is effective against SARS-COV-2 when used in combination with ritonavir. It inhibits replication of virus in host cell. Common side effects: diarrhea, headache, vomiting, nausea, etc. |
| Ritonavir                  | Similar to lopinavir, ritonavir is also an antiviral currently used against HIV. It has also potential against SARS-COV-2 when used in combination with lopinavir. It inhibits replication of virus in host cell. It has similar side effects as that of lopinavir. |
| RDV                        | A nucleoside analog. It was prepared for treatment of Ebola Virus. It inhibits replication of virus in host cell. RDV is prodrug becomes active in side human cell for Covid-19. Side effects: Liver damage, nausea, vomiting RDV’s Active metabolite, GS-441525. It inhibits replication of virus in host cell |

(continued on next page)
Table 1 (continued)

| Structure and name of drug |
|---------------------------|
| Remarks                   |
|                           |

- **Remdesivir**: Prodrug
- **Active form**: Remdesivir
- **Darunavir**: Protease inhibitor. The coronavirus responsible for COVID-19, due to in vitro evidence supporting its ability to combat this infection. Clinical trials are underway and are expected to conclude in August 2020. It inhibits replication of virus in host cell.
- **Ribavirin**: Nucleoside analog antiviral agent. For treatment of COVID-19 its high concentration is needed than remdesivir. It inhibits replication of virus in host cell. The common side effects: nausea, fevers, inflammation, headache etc.
- **Favipiravir**: Prodrug antiviral agent. RdRp inhibitor, RNA induced Lethal Mutagenesis. It inhibits replication of virus in host cell. Side Effects: During pregnancy may result in harm to the baby.
- **Glycyrrhizin**: Extracted from the root of the licorice plant; Glycyrrhiza glabra. It is a triterpene glycoside with glycyrrhetinic acid that possesses a wide range of pharmacological and biological activities. It inhibits replication of virus in host cell and inhibits toxic molecule release.
- **Disulfiram**: Blocks an enzyme that is involved in metabolizing alcohol intake. In Covid-19, inhibits toxic molecule release. Disulfiram produces very unpleasant side effects when combined with alcohol.

(continued on next page)
Table 1 (continued)

| Structure and name of drug | Remarks |
|---------------------------|---------|
| ![Disulfiram](image)       | Omeprazol specially developed for influenza virus. It inhibits Nuraminidase Enzyme (inhibits Eocytosis) Side effects: Irregular heart beat, arm pain etc. |
| ![Oxetamivir](image)       |         |

3.2. Vaccines to control the Covid-19

There are mainly four types of vaccines to control Covid-19 as given below.

(i) RNA Vaccines: This vaccine uses a copy of mRNA and produces an immune response.
(ii) Adenovirus vector vaccines: These are non replicating viral vector vaccine, it presents antigen which elicits a systemic immune response.
(iii) Inactivated virus vaccines: These consist of viral particles (killed by heat or formaldehyde to lose disease-producing capacity while still stimulating an immune response)
(iv) Subunit vaccines: These present one or more antigens, and antigens involved are often protein subunits but can be any molecule that is a fragment of the virus.

Except above four types of vaccines, other types of vaccines that are in chemical trial are virus-like particle vaccine, DNA plasmid vaccines, lentivirus vector vaccine, conjugate vaccines and vesicular stomatitis virus. There are 14 vaccines authorized by regulatory authorities and belong to mainly the above four types. A description of each vaccine is given in Table 2.

4. Green approaches to counter viral infections

4.1. Review of literature on the antiviral activity of natural extracts

The commonly used allopathic medicines or so-called modern medicines have found significant praise because of their fast action and potency. However, their continuous usage can cause a patient to develop immunity against the same. In addition, these drugs have also been known to cause several side effects, despite being too expensive [4–6]. On the other hand, the medicines having natural origin although have been criticized for having slower action; still, most of these have almost negligible side effects [7,8]. The medicinal plants and herbs contain bioactive metabolites that have pharmacological properties. Therefore, these alternatives present a natural source of cheaply available drugs having less harmful effects [38]. The plant products have antioxidant activities due to the presence of phenolic compounds. These compounds have potential antimicrobial activity, thereby imparting excellent medicinal properties to plant-based drug products. The different antiviral mechanisms of the plant-based medicines have been identified against some of the notable viral pathogens, including the coronavirus, cox-sackievirus, dengue virus, enterovirus, herpes virus, influenza virus, measles virus, etc. [39,40]. It has also been identified that in which part of the viral life cycle these medicinal products interact with them, e.g., entry, replication, release, etc. Several articles are available in the literature on the antibacterial, antifungal, etc., activities of the naturally-derived extracts, etc. Herein we have gathered a collection of literature showing the antiviral activity of the natural extracts derived from various herbs and medicinal plants as detailed vide infra.

Various polyphenols, flavonoids, and alkaloids have been isolated from plants and used as anti-influenza agents [41]. Polyphenol extract derived from Geranium sanguineum L. has shown potential anti-viral activity along with antioxidant and radical scavenging capabilities [42]. Bioflavonoid ginkgo was isolated from Gingko biloba L. and Cephalotaxus harringtonii K., and have shown significant anti-influenza activity [43,44]. Medicinal plants such as Berberis ligulata, Nerium indica, and Holoptelia integrifolia have shown anti-influenza activity [45]. Lignans derived from Rhinacanthus nasutus have also exhibited anti-fluence activity [46]. S. alopecuroides L., S. flavescens and S. subprostrata (shandougen) contain alkaloids, namely oxymatrine and matrine, and have shown to inhibit viral replication in case of hepatitis C virus [47–51]. A. nilotica, B. carterii, E. schimperi, Q. infectoria, P. cubeba, T. ammi, and S. aromaticum have shown effective performance against HCV [52]. Essential oils derived from Santolina insularis have shown effective performance against the herpes virus [53]. Several plants have been screened for ethnomedical backgrounds for antiviral activity against the herpes virus without having any toxic effects on cells [54]. H. integrifolia and N. indica have shown considerable activity against the herpes virus without showing any significant toxic influence against the cells [45].

The flavonoids have shown considerable antiviral activity. The antiviral activity of the flavonines has been known since 1990s [55]. Apigenin from sweet basil has shown significant activity against adenoviruses and hepatitis B virus [56]. In addition, apigenin has also shown activity towards suppression of protein synthesis in African swine fever virus (ASFV) [57]. The reduction of mature microRNA122 of HCV has been displayed by apigenin [58]. Baicalein and luteolin are other flavones that have been investigated for their antiviral activity. Baicalein considerably reduced the protein synthesis in the human cytomegalovirus (HCMV) and the viral DNA synthesis [59]. It also impaired the replication of avian influenza H5N1 virus in human epithelial cells [60]. Baicalein and baicalin exerted significant antiviral influence against the dengue virus (DENV) while interfering with the various steps of the virus replication [61–63]. Luteolin has shown antiviral activity against HIV-1 reactivation [64]. It also shows significant inhibition activity against Epstein-Barr virus (EBV) reactivation by suppressing the related genes in the early stages [65]. Luteolin or luteolin-rich fractions have also shown considerable antiviral activity against the SARS-CoV, rhesus rotavirus, and Japanese encephalitis virus (JEV) [66–68].

Among the flavonoids, the antiviral effect of quercetin has been the most widely investigated. Oral treatment of mice with quercetin...
provided protection from the Mengo virus [69,70]. Quercetin, in combination with the murine type I interferon (IFN) provided enhanced protection [71]. Dose-dependent antiviral activity of quercetin was observed against poliovirus type 1, HSV-1, HSV-2, and respiratory syncytial virus (RSV) [72,73]. Quercetin has also shown to reduce the Newcastle disease virus (NDV) replication, vesicular stomatitis virus (VSV) as well as some of the influenza viruses [74]. Computational studies have shown that quercetin can considerably inhibit the neuraminidase of influenza A H1N1 and H7N9 viruses [75,76]. Kaempferol and its several derivatives having acyl functionality have shown considerable performance against the HCMV [77]. Its derivatives extracted from Ficus benjamina leaves have shown effective antiviral behavior against HSV [78].

2-phenyl-3,4-dihydro-2H-chromene skeleton is the characteristic of flavans. Among these, the antiviral activity of the catechins and their derivatives, such as epicatechin, epicatechin gallate, epigallocatechin (EGC), and epigallocatechin gallate (EGCG) have been considerably investigated [79]. The tea catechins have also shown antiviral activity against HIV-1 [80,81]. EGCG and ECG have shown effective action in the inhibition of the HIV-1 reverse transcriptase in vitro [82,83]. A significant activity of the tea catechins has also been shown against the herpes viruses [84]. Soybeans and fava beans contain an isoflavonoid named Genistein, which functioning as a tyrosinase inhibitor, reduced bovine serum herpesvirus type 1, and New World arenavirus Pichinde replication [85,86]. It has also been shown to inhibit the HIV infection of the resting CD4 T cells and macrophages [87].

### 4.2. Innovations in the delivery and bioavailability of phytochemicals

The introduction of organic synthesis from the areas of pharmaceutical chemistry, multicomponent synthesis strategies, nanomaterial preparation, etc., has paved the way towards chemical functionalization of the phytochemical constituents derived from the natural extracts [88]. These innovations have improved the pharmacokinetic and clinical output of the phytochemical-based drug systems. The approaches that have been commonly used as phytosomes, hydrogel formation, nanoscience, microspheres, transferosomes, ethosomes, etc., have improved the delivery of plant-based antiviral agents. Although, here it is important to note that only a few studies are available in the literature on the application of natural extract-based drug delivery systems or so-called herbal drug delivery systems. However, in this section, we have outlined a few of the successful attempts in this area. Flos Lonicerae Japonicae and Fructus Forsythia are commonly used Chinese herbal remedies. They have been further chemically modified using a chitosan oligosaccharide to improve the bioavailability and the anti-influenza activity [89]. The oral bioavailability of apigenin was increased by using soybean oil-Tween 80 emulsion system, which was applied on the animal model in addition to the particle size estimation and the zeta potential measurements [90]. The oral absorption of baicalin was improved using a micellar formulation comprising a copolymer and sodium taurocholate [91]. Oleoanic acid solubility was increased using a formulation consisting of 50% ethyl oleate, 35% Cremophor EL, and 15% alcohol. This resulted in a sustained released behavior and improvement in the systemic rat bioavailability [92]. The bioavailability of a herbal drug was improved using honokiol and sulfobutyl ether-β-cyclodextrin. The in-vitro results showed an enhanced release was observed [93]. PLGA (poly (lactic-co-glycolic acid)) was used to develop andrographolide microspheres to improve its oral bioavailability [94].

### 5. Application of phytochemicals in countering the Covid-19

The non-availability of the Covid-19-targeted conventional therapeutics such as vaccines, antibiotics, etc., has led to the use of broad-spectrum antibiotics and well-established antiviral treatments. Herein, the extracts derived from the natural products that are the rich source of the active compounds can be utilized effectively against the coronavirus [95]. Extracts derived from several traditional Chinese medicinal plants have been observed to inhibit the replication of SARS-CoV. Over 200 extracts were investigated in a study, and their potency was established in countering the SARS-CoV [96]. Bioflavonoids derived from Torreya nucifera were found to successfully inhibit the replication of SARS-CoV 3CL pro [97]. The ethanolic extract derived from the leaves of this plant showed 62% inhibition activity at 100 μg/L concentration. Using the fluorescence resonance energy transfer (FRET) method, eight diterpenoids and four bioflavonoids were identified as potential inhibitors. The experimental results of the enzymatic tests were supported by the
Table 3
Medicinal plants as anti-corona agents.

| Drug               | Herb                  | Remarks                                                                 |
|--------------------|-----------------------|-------------------------------------------------------------------------|
| 6-Gingerol         | Ginger (Zingiber officinale) | Strong antiviral, Supports Immune system, reduce risk of diabetes and cancer |
| Demethoxy curcumin | Turmeric (Curcuma longa) | Strong Antiviral, Anti-Inflammatory, Protect Against Heart Disease, Protect Against Heart Disease |
| Allicin            | Garlic (Allium sativum) | Proteolytic and hemagglutinating activity and stop viral replication, Cold and Flu, Anti-bacterial and Anti-parasitic, Prevention of Heart Disease, Cancer Prevention. |
| Quercetin          | Onion (Allium cepa)    | Strong antiviral, Cancer prevention, Skin and hair, Blood pressure moderation. |
| Quercetin          | Green Chilli (Capsicum annum) | Strong antiviral, anti-cancer, anti-inflammatory |
| Andrographolide    | Green Chireta, creat (Andrographis paniculata) | Antiviral and anti-inflammatory, inhibits the replication of influenza virus, decreases inflammation of lung, prevents the damage of liver cells |
| Eugenol            | Holy basil (Ocimum tenuiflorum) | Anti-Viral |

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molecular docking analysis [97]. The extracts from *Houttuynia cordata* Thunb. containing quercetin, quercitrin and cyanserine was assessed for the antiviral activity in the coronavirus and dengue virus infections in mice via the *in vitro* tests [98]. These flavonoids were evaluated for their efficacy against the mouse coronavirus and dengue virus in the virus neutralization tests and acute oral toxicity in the mice. The IC50 of the extracts was 0.98 mg/mL and 7.50 mg/mL for coronavirus and the dengue virus, respectively. Up to 2000 mg/kg oral doses fed to the mice did not produce any acute toxicity. Furthermore, a synergistic activity of quercetin and quercitrin was observed in the antiviral activity [98]. Against the MERS-CoV-3 coronavirus, the potential activity of flavonoids was characterized [99]. The compounds, namely herbacetin, isobavachalcone, quercetin 3-β-d-glucoside, and helichristetine, were found to successfully block the enzymatic activity of the MERS-CoV-3 coronavirus. Flavonoids having hydrophobic or carbohydrate groups were used as inhibitors against the MERS-CoV 3CL Pr [99]. Flavonoids were also investigated by Nguyen et al. against *Pichia pastoris* with the acute respiratory syndrome (SARS-CoV) [100]. The synthesis and antiviral action of some quercetin derivatives were evaluated against SARS-associated coronavirus (SCV) and hepatitis C virus (HCV) [101]. The structure-activity studies of the quercetin-3-β-galactoside and its derivatives were evaluated against the SARS-CoV 3CL Pr using the structure-activity relationships [102]. The quercetin-3-β-galactoside had the potential as an anti-SARS drug and helped in the elucidation of the mechanism of inhibition against the targeted enzyme. The *Sambucus Formosana Nakai* extract provided excellent anti-HCoV-NL63 potential by the activity of the phenolic acid components that included the coffee acid, chlorogenic acid, and gallic acid [103]. The polyphenolic components present in the green tea have been shown to provide antiviral effect [104]. The leaf extracts of *Toona sinensis Roem* provided inhibition activity to SARS-CoV [105]. The flavonoids existing in *Galla chinensis* or *Veronica linrifolia* extracts have shown the binding capability to the surface spiky proteins of the SARS virus preventing its penetration to the cell [106]. The experimental studies were supported by the molecular docking analysis. The aqueous extracts of the *Isatis indigotica* root contain several phenolic compounds and have shown anti-SARS-CoV 3CL Pr
Some of the medicinal plants and their phytochemical constituents that could be potential anticoagula agents are listed in Table 3.

Yi et al. studied the influence of the phytochemical components of flavonoids and polyphenols on the entry of SARS-CoV [68]. Reserpine and Aescin showed the interference to block the entry of the virus inside the cells and have shown the inhibition of the activity of the 3CLpro enzyme of the virus [108]. Lectins isolated from different plants have shown a considerable anti-SARS-CoV activity [109]. Emodin has shown the inhibition of the 3a ion channel of coronavirus and has shown to inhibit the release of the SARS-CoV from the infected cells [110]. Griffithsin, the protein extracted from the red algae Griffithsia, has been shown to be effective against the MERS-CoV [111]. Here it is noteworthy to mention that the Griffithsin has a high specificity index towards the human coronavirus [112], which suggests its high applicability in clinical trials as well as usage in animal model studies. Saikosaponins (A, B2, C, and D) that are derived from plants displayed good to moderate antiviral potential against HCoV-229E [113]. The methanolic extract of the leaves of Strobilanthes cusia has shown an effective reduction in the virus in the infected cells [114]. Tryptanthrin is a naturally occurring alkaloid having the basic indolepyrimidine moiety that exhibited high antiviral activity against HCoV [115]. The tryptanthrin has also been shown to inhibit the early and late replication periods of HCoV-NL63 [116]. Silvestrol was investigated in an ex vivo study of the bronchial epithelial cells to the inhibition of RNA helicase eIF4A [117]. Qingfei Paidu Decoction (QFPD) consisted of a total of 21 components, including the herbs and mineral drugs, and produced an effectiveness of 92% among the patients at all the stages, including the cured and the discharged, wherein the clinical symptoms disappeared, and patients showed stability and improvement [118].

A fruitful approach in developing an understanding of the performance of a natural product is the use of bioinformatics studies. The computational analysis has shown considerable support in the identification of the best available drug candidates. Besides, the computational studies have also shown their application in the exploration of the genetic pathways of the antiviral metabolites of natural products. The computational modeling studies have also allowed the virtual screening of the SARS-CoV-2 inhibitors. The bioinformatics approach plays a crucial role in identifying the potential antagonistic compounds that can target the binding sites of the SARS-CoV viral proteins via complex molecular interactions for viral attachment and replication [119,120]. The computational assistance has led to a rise in the pace of the research and development ongoing in the exploration of the SARS-CoV-2 solutions. The design and the synthesis of the novel compounds that can play an important role against the Covid-19 can be facilitated using computational studies. The correlation of the structural features of the novel inhibitory compounds with their inhibition potency can be characterized using molecular docking studies [75,76,121]. The molecular dynamics simulation is a viable tool in this context. Earlier, these studies have shown the screening of the binding affinity of several flavonoids by identifying the role of the different functional groups that take part in the interaction. In addition, several databases have been available such as the National Center for Biotechnology Information (NCBI), and Kyoto Encyclopedia of Genes and Genomes (KEGG), The Arabidopsis Information Resource (TAIR), Medicinal Plant Database for Drug Designing (MPD3), and the International Ethnobotany Database (eBDB). These databases have provided specific and useful information of medicinal plants and their metabolic pathways. It is important to note that some of these are non-commercial repositories and even provide free of cost information regarding the strong structure and data export features. In some cases, comprehensive information about the detailed structure and potential activities of the phytochemicals are also available.

6. Conclusions and prospects

The Covid-19 pandemic is an unprecedented event in the course of history. It has led to a huge loss of human life and has produced a large-scale economic and sociological impact all over the world in different sections such as healthcare, business, education, sports, entertainment, travel, and tourism, etc. Since the onset of the pandemic, there has been research and development in the area of cure as well as prevention in the form of medicines and vaccinations; however, in most cases, not much promise has been observed. Although recently, fortunately, few medicines and vaccination treatments have been coming across, still, there are cost factors associated which restrict the easy availability of these solutions to the target public. Furthermore, the use of modern medicine has been often criticized due to the associated side effects.

In this case, the prime objective of this review article is to provide an overview of some of the antiviral medicines based on the plant products that have produced significant performance. The naturally derived bioactive compounds function as antioxidants, direct enzyme inhibitors, and block the surface protein receptors in the virus. A variety of medicinal plants have been shown to have a considerable source of phytochemicals and have exhibited a wide range of bioactivity. Therefore, it is proposed herein that these drugs could provide useful alternatives compared to the modern medical treatment of the Covid-19. The research articles collected in this review show that the medicinal plants exhibit promising therapeutic potential, especially against viral infections, which is the focus of the present review. Some concerns have been raised against the reaching of the plant-based medicines to the target virus. In this context, the development in the area of nanoscience and drug delivery systems has shown promising progress. Although there are numerous systems available on modern drug-delivery technologies, however, this area is still currently at the growing stage in the context of herbal medicines, and much progress has to be achieved. The phytochemical-based components discussed herein have provided hope that the Covid-19 pandemic can be tackled based on the Green Chemistry-based approaches that can afford an effective solution as well as an environmentally sustainable health care practice.

Disclaimer

The authors alone are responsible for the content and writing of the paper.

Author contributions

Dr. DS Chauhan and Dr. S Yadav drafted the manuscript and prepared the Figures and Tables. Prof. MA Quraishi did the data analysis and critical revision.

Funding sources

No funding support was received.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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