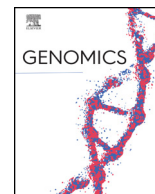




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Minireview

Genomics approaches to synthesize plant-based biomolecules for therapeutic applications to combat SARS-CoV-2



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ABSTRACT

COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is devastating to the humankind for which neither vaccines nor precise therapeutic molecules for treatment are identified. The search for new drugs and repurposing of existing drugs are being performed; however, at the same time, research on plants to identify novel therapeutic compounds or testing the existing ones is progressing at a slower phase. In this context, genomics and biotechnology offer various tools and strategies to manipulate plants for producing those complex biopharmaceutical products. This review enumerates the scope for research on plant-based molecules for their potential application in treating SARS-CoV-2 infection. Strategies to edit gene and genome, overexpression and silencing approaches, and molecular breeding for producing target biomolecules in the plant system are discussed in detail. Altogether, the present review provides a roadmap for expediting research on using plants as a novel source of active biomolecules having therapeutic applications.

1. Introduction

Advancement of civilization at a rapid pace faces the spread of complex diseases and infections that threatens the human race. Among the diseases, several pandemics have wiped a predominant human population throughout history. To note a few, flu, plague, pox, yellow fever, malaria, leprosy, tuberculosis, measles, dengue, HIV/AIDS, H1N1, SARS, Ebola, and MERS were disastrous. Among these, the present-day COVID-19 (caused by Severe acute respiratory syndrome coronavirus 2; SARS-CoV-2) is potentially contagious and lethal that has forced almost all the countries to practice a strict lockdown for minimizing the spread [69]. The virulence of this virus, along with the evolution of different strains, has urged the scientific community to identify vaccines, therapeutic drugs, and diagnostic methods for rapid detection, treatment, and immunization of the human population. Though progress has been made in the development of biological- and chemical-based strategies to diagnose the disease, there is no drug or vaccine invented so far to treat the infected patients effectually [55]. The appearance of disease symptoms at a late stage and the issue of asymptomatic infections have constrained the diagnosis procedures; however, testing the entire population for the virus infection holds the key to identify the infected ones, isolate and treat them in a suitable way (WHO, 2020). In case of treatment of infected patients, the use of

existing antiviral drugs is prevalent, and also, repurposing of drugs is suggested for testing and application. Currently, antiviral drugs such as Lopinavir/Ritonavir and Remdesivir are predominantly used in the treatment. These commercially synthesized molecules inhibit the virus replication either by regulating the ion channel transport or inhibiting the serine protease activity [16,97]. However, the search for novel compounds that could interfere with viral replication, assembly, and spread within the human system is in progress. Devising new molecules through computational and integrative approaches that target one or the other process of virus infection and spread could be an amenable strategy. Still, the chemical synthesis of such a molecule is time-consuming and labor-intensive. Screening of existing molecules for repurposing is already being carried out, but at the same time, studying the plants for novel phytochemicals that possess potential antiviral activity is largely ignored.

Large-scale screening of plants for active antiviral compounds dates to 1952, where around 288 plant extracts were tested for their activity against influenza A virus [11]. Later, Debiaggi et al. [19] had shown the antiviral effect of *Chamaecyparis lawsoniana* on herpes simplex virus type 2. Similarly, Serkedjieva [78] identified the antiviral effect of *Geranium sanguineum* extract against influenza A virus, and Asres and Bucar [3] showed anti-HIV activity of *Combretum mole*. An aqueous extract of *Agrimonia eupatoria* and root extract of *Boehmeria nivea* were

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Table 1
Plant-based compounds reported to possess antiviral activity.

Plant	Compound	Target	Mode of action	Reference
<i>Allium sativum</i>	Allyl disulfide	S protein	ACE2 receptor inhibitor	[87].
<i>Anethum graveolens</i>	Quercetin	main protease (M ^{Pro})	Virus replication	[37]
<i>Artemisia annua</i>	Aurantiamide acetate	Inhibition of CoV protease	Virus replication	[63]
<i>Broussonetia papyrifera</i>	3'-(3-methylbut-2-enyl)-3',4,7-trihydroxyflavone	Inhibition of CoV protease	Virus replication	[66]
<i>Camellia sinensis</i>	3-Isotheaflavin-3-gallate	main protease (M ^{Pro})	Virus replication	[12]
	Theaflavin	RNA-dependent RNA polymerase	Virus replication	[54]
<i>Cinnamomi sp.</i>	Procyanidin A2	–	Inhibition of virus entry	[108]
<i>Curcuma longa</i>	Demethoxycurcumin	main protease (M ^{Pro})	Virus replication	[37]
<i>Dioscoreae Rhizoma</i>	–	–	Inhibition of virus growth	[99]
<i>Galla chinensis</i>	Tetra-O-galloylβ-D-glucose	S protein	ACE2 receptor inhibitor	[102]
	Luteolin	Spike protein	Virus entry	
<i>Griffithsia sp.</i>	Griffithsin	Spike protein	Inhibition of virus entry	[59]
<i>Isatis indigotica</i>	Aloe emodin	main protease (M ^{Pro})	Virus replication	[49]
<i>Linum usitatissimum</i>	Herbactin	main protease (M ^{Pro})	Virus replication	[36]
<i>Lycoris radiata</i>	Lycorine	–	Inhibited cell division	[79]
<i>Malus domestica</i>	Apigenin	main protease (M ^{Pro})	Inhibited virus replication	[76]
<i>Olea europaea L.</i>	Luteolin-7-glucoside	main protease (M ^{Pro})	Virus replication	[37]
<i>Averrhoa belimbi</i>				
<i>Capsicum annum</i>				
<i>Allium fistulosum</i>				
<i>Rheum officinale</i>	Emodin	Inhibited binding of S protein to ACE2	Virus entry	[88]
<i>Salvia miltiorrhiza</i>	Tanshinone IIA/B	Inhibition of CoV protease	Virus replication	[65]
<i>Salvia officinalis</i>	Safficolide	main protease (M ^{Pro})	Inhibited virus replication	[76]
<i>Stephania tetrandra</i>	Tetrandrine	S and N protein	Virus replication	[40]
<i>Torreya nucifera</i>	Amentoflavone, Apigenin	main protease (M ^{Pro})	Virus replication	[109]
<i>Tripterygium regelii</i>	Celastrin	Inhibition of CoV protease	Virus replication	[74]
<i>Urtica dioica</i>	agglutinin	Spike protein	Inhibition of virus entry	[45]

– ‘No information available.

reported to inhibit hepatitis B virus [32,47]. Kotwal et al. [43] had demonstrated that an acidic extract of *Trifolium* species could show a broad-spectrum antiviral activity, including anti-SARS activity. Thus, examining natural antiviral compounds from plants gains momentum in the present scenario. These plant-based therapeutic drugs have several advantages as compared to synthetic molecules. Naturally available biomolecules are safe, economical, and have minimal side effects. Further, if a plant-based compound is found to regulate the COVID-19 infection, it can facilitate an immediate use in the treatment regime after obtaining necessary ethical clearances. However, these compounds might not be stable or produced at minimal levels since they might play limited roles *in planta*. A holistic approach is required to identify such potential compounds, study the biosynthesis pathway, analyze the genes underlying those pathways, and finetuning them using genomics and biotechnological interventions could promote the use of plants as a source and bio-manufacturer of antiviral compounds in large-scale. While mainstreaming plant-based research to identify biomolecules having anti-SARS-CoV-2 activity itself is in a nascent stage, exploiting the potential plants as biofactories is a long way to go. However, the advent of tools and techniques in plant molecular biology and biotechnology could expedite this process provided a roadmap need to be established towards achieving these targets. Given this, the present review enumerates the plant-based compounds that have been identified and characterized so far for treating viral infections with emphasis on coronavirus strains. The strategies for the identification of additional compounds, implementing omics tools for the over-production of those compounds, customization of biomolecules, and scaling-up of the process for large-scale production have been elaborated. Altogether, the review provides a roadmap for extrapolating the biomolecule repertoire of plants and use genomics and biotechnological approaches for their production and effective use in SARS-CoV-2 treatments.

2. Plant-based biomolecules with antiviral activities

Presently, traditional medicines from different parts of the world have been studied for their therapeutic effect against SARS-CoV-2.

Traditional medicines-based defense methodology has been used against different human viruses, including SARS-CoV, Ebola, and Zika viruses [101]. Recently, Sehailia and Chemat [77] had compared the mechanism of infection of SARS-CoV-2 and malaria plasmodium and found that both the pathogens infect the lungs to cause the crystallization of carbon dioxide. Based on this information, artemisinin molecule (sesquiterpene lactone), isolated from *Artemisia annua*, has been proposed to be used in the treatment of SARS-CoV-2 patients. Artemisinin is popularly used in treating malaria; however, it has also been tested for its activity against different viral diseases, including MERS-CoV and SARS-CoV [18,27]. Currently, WHO has backed the clinical trials on *Artemisia annua* for its use in treating COVID-19, and collaborative research in this direction is being performed at Max-Planck research center, Germany and Mateon Therapeutics, California. The use of medicinal plants for treating infectious diseases is found to be associated with the tradition and custom of several populations around the globe. For example, Traditional Chinese Medicine (TCM) is one of the well-studied and documented practices followed in China that has been reported to cure many diseases or infections, including SARS-CoV [51,89,104]. Approximately 85% of COVID-19 patients were treated with TCM that might act due to a close homology between SARS-CoV-2 and SARS-CoV [101]. These plants could possess active biomolecules that regulate virus accumulation by restricting their multiplication. For example, flavonoids (herbactin, isobavaschalcone, rhoifolin, pectolinarin, quercetin 3-β-D-glucoside, and epigallocatechin gallate) were found inhibit the enzymatic activity of one of the viral proteases; MERS-CoV 3CL protease and myricetin and scutellarein have the potential to regulate the helicase activity of nsP13 (SARS-CoV helicase protein). Yang et al. [101] had reported that at least fifteen clinical trials are underway to test the efficacy of TCM in treating SARS-CoV-2 infection.

Countries other than China focus very less on their traditional medicinal plants that could be a potential source of active antiviral molecules. For example, India has a long record of using plants in treating virus-induced respiratory diseases; however, further research towards pinpointing the molecules having roles in antiviral activity is limited. A few Indian collections of medicinal herbs were reported to demonstrate anti-inflammatory and antioxidant properties and can be

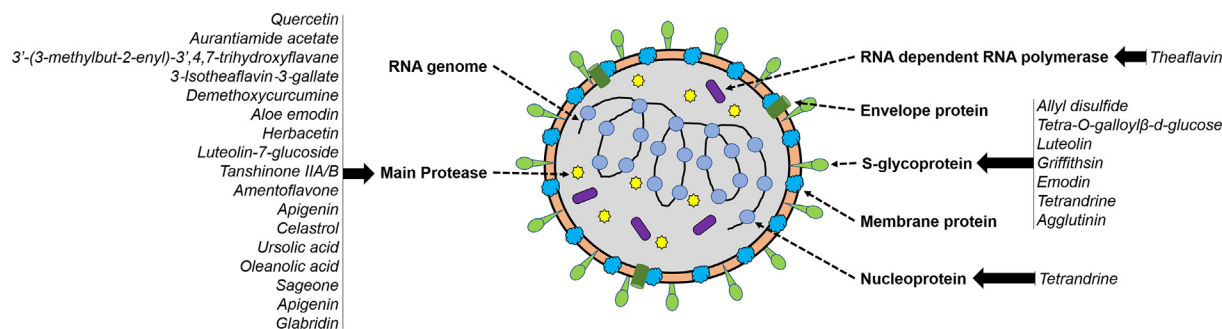


Fig. 1. Structural proteins of SARS-CoV-2 and the potential plant-based biomolecules interacting with these proteins. The mode of action of these biomolecules are given in Tables 1 and 2.

used for the treatment of COVID-19 [92]. For instance, *Vitex trifolia* and *Sphaeranthus indicus*, the medicinal plants from Southern India, have been reported to target cytokines, thus reducing the inflammation during respiratory diseases, including SARS-CoV at a concentration of 400 ng/mL [86]. Similarly, several species used in the daily diet contain metabolites such as curcumin and quercetin, which were found to interact with proteases of SARS-CoV-2 [76]. Further, Unani medicine, having an antiviral effect against measles and similar virus disease, has been proposed to provide an inhibitory effect on SARS-CoV-2 [62]. The antiviral compounds reported so far in plant species are summarized in Table 1, and their target sites of action on SARS-CoV-2 are shown in Fig. 1. In addition to antiviral activity, plant extracts also possess antioxident, antipyretic, anti-asthmatic, bronchodilator, expectorant, analgesic, and anti-inflammatory activities that have application in the treatment regime of respiratory diseases (Table 2). Several herbs have been reported to possess immune-boosting properties, and this includes *Ocimum tenuiflorum*, *Zingiber officinale*, *Trigonella foenum-graecum*, *Allium sativum*, and *Curcuma longa*. However, there is no comprehensive study performed to identify the active biomolecules that interact with the immune system of the human body to enhance the resistance to diseases. The prevalence of COVID-19 as a pandemic has mandated research and development for identifying vaccines, therapeutic and diagnostic molecules; however, such searching for those biomolecules in plants is not being performed at the right pace. In case of plant-based vaccines, research is appropriately being carried out to express novel virus-like particles (VLP) in plants that could serve as potential antigens for eliciting immune responses. The prime advantages of plant-based vaccines are their purity (free from human pathogens), low cost for production, transportation, and storage [70]. In case of diagnostic reagents, plants serve as a suitable host for expressing viral proteins to develop assay kits for effective detection and diagnosis of SARS-CoV-2 (reviewed in [10]). Given this, the review explicitly covers the identification and isolation of plant-based therapeutic molecules and the role of genomics and biotechnology in reaping the maximum benefit out of plants for effective treatment of potential diseases.

3. Identification of novel therapeutic biomolecules in plants

Plants could serve as a reservoir of potential drugs and therapeutic molecules, and an integrated approach is required to identify and characterize those molecules. Proteomic and metabolomic profiling using high-throughput platforms are a boon for large-scale analysis of plant extracts to identify the biomolecular composition of those extracts. A comprehensive review of literature that exists in use within the community or population can help to identify the potential plants that can be targeted for metabolic screening. Predominantly, metabolites possess therapeutic properties than the simple protein molecules which are reported to be involved in cellular and biological processes of plants. Sampling of plants at different stages of development, preparation of tissue-specific extracts (using different solvents), and

analysis of those extracts using Gas and/or Liquid Chromatography-Mass spectrometry can identify metabolites and other volatile compounds present in the extract. High-Performance Thin-Layer Chromatography can assist in fingerprinting of secondary metabolites and separating those metabolites at high-resolution. Computational tools coupled with these platforms, aid in the identification of the metabolites, whose chemical structure can be resolved at high-resolution using several available *in silico* approaches. For screening the efficacy of these biomolecules and studying the potent inhibitors against coronavirus, computer-aided drug design (CADD) serves as a reliable approach [96,107] as it facilitates a multidimensional study of molecular interactions between putative anti-COVID-19 compounds and target proteins. This approach has suggested the interaction of SARS-CoV-2 encoded proteins with different phytochemicals. 3C-like protease (3CL^{Pro}), also known as Main protease (M^{Pro}) is an attractive target for anti-CoV drug design. It is a cysteine protease and is responsible for cleaving the replicase polypeptide into various functional proteins and essential for virus multiplication. Phenolic compounds such as coumarin, flavones [39], baicalin, cyanidin 3-glucoside, and α -ketoamide-11r [34] have structural similarity with the protease and might be the potential and safer inhibitors against the SARS-CoV-2. Apart from this, the Moroccan Medicinal plants containing Crocin, Digitoxigenin, and β -Eudesmol were projected as COVID-19 inhibitors based on the computational investigation with a benefit of oral intake [1]. Phytochemicals such as Belachinal, Macaflavanone E, and Vibsanol B have been found to restrict the formation of ion channels by oligomerization of 'SARS-CoV2 E', thus inhibiting the virus pathogenesis [25].

The interaction between Spike (S) Glycoprotein of SARS-CoV-2 and angiotensin-converting enzyme 2 (ACE2) receptor is crucial for the entry of SARS-CoV-2 into the human alveolar epithelial cells. Different plant-derived lectins such as Griffithsin and *Urtica dioica* agglutinin lectin interact with S protein and inhibit the binding onto the host cell [45,59]. Simultaneously, phytoestrogens, especially Diadiazin, Genistein, Formononetin, and Biochanin A were found to have a high affinity towards the substrate-binding domain β (SBD β) of Heat Shock Protein A5 (HSPA5). It is the host-cell receptor that interacts with S protein of COVID-19 and leads to the entry of the pathogen into the host cell. These phytoestrogens have been reported to act as competitive inhibitors against Spike protein by binding onto the active site of HSPA5 [21]. Recently, *Withania somnifera* compound, Withanone (Wi-N) was found to weaken the binding between ACE2-RBD complex and was thus proposed to control the virus entry into the host cell [7]. Kumar et al. [46] had also shown that Wi-N and caffeic acid phenethyl ester of *W. somnifera* interact with the highly conserved protease, M^{Pro} of SARS-CoV-2. These reports justify that plant-based anti-COVID drugs could save time and cost for designing/developing new therapeutic molecules; however, large-scale screening of plants for identifying such potential biomolecules is imperative. Such compounds once identified will be processed to the further steps for laboratory trials and clinical trials followed by large-scale production, purification, and application

Table 2
Potential plant-based biomolecules useful for therapeutic applications to treat SARS-CoV-2.

Compound	Source	Class	Mode of action	Reference
Anti-asthmatic compounds				
1,8-Cineol	<i>Eucalyptus globulus</i>	Monoterpene	NF- κ B p65 translocation to nucleus is inhibited thus, hampering NF- κ B mediated transcription.	[24]
3-Methoxy-catalposide	<i>Pseudobulbinachion rotundum</i>	Iridoid glycoside	Inhibitory effect on lipopolysaccharide stimulated RAW264.7 macrophages.	[73]
7-Glucuronic acid-5,6-dihydroxyflavone	<i>Scutellaria baicalensis</i>	Flavonoid	Inhibitor of phosphodiesterase 4A and 4B. Downregulates the expression of TNF- α .	[67]
5,7-dihydroxyflavon	<i>Passiflora caerulea</i>	Flavonoid	Suppression of mast cell mediated release of pro-inflammatory cytokines.	[6]
Crocin	<i>Croctus sativus</i>	Carotenoid	Asthma mitigation by activation of Foxp3 through T1PE2 in asthma associated Treg cells.	[20]
Curcumin	<i>Curcuma longa</i>	Polyphenol	Inhibition of Notch1–GATA3 signalling pathway preventing the development of allergic airway inflammation.	[15]
Diallyl- disulfide	<i>Zingiber officinale</i>	Organosulphur	Suppression of airway inflammation by activation of Nrf-2/HO-1 pathway and downregulation of NF- κ B.	[82]
D- α -tocopheryl acetate	<i>Glycine max</i>	Vitamin	Modulates atopic asthma and inhibits oxidative stress.	[31]
Ellagic acid	<i>Rubus fruticosus</i>	Polyphenol	Inhibition of NF- κ B mediated transcription	[106]
1,3,8-Trihydroxy-6-methylanthraquinone	<i>Rheum palmatum</i>	Anthraquinone	Inhibition of NF- κ B signalling pathway	[83]
Homoeogonol	<i>Syrax japonica</i>	Lignan	Reduction in the number of inflammatory cells and Th2 cytokines	[81]
Kaempferol-O-rhamnoside	<i>Camellia sinensis</i>	Flavonoid	Reduction in the number of inflammatory cells and Th2 cytokines	[17]
L-Theanine	<i>Camellia sinensis</i>	Amino acid	NF- κ B and MMP-9 levels are reduced leading to anti-inflammatory activity	[33]
Luteolin	<i>Perilla frutescens</i>	Flavonoid	Airway mucus accumulation is inhibited by inhibition of GABAergic system	[80]
Mangosteen	<i>Garcinia mangostana</i>	Xanthone	Inhibition of cytokine production and histamine release	[35]
Naringin	<i>Citrus paradisi</i>	Flavone	Induction of calcium signalling leading to bronchoconstriction inhibition	[98]
Oxymatrine	<i>Sophora flavescens</i>	Alkaloid	Anti-asthmatic effect by regulation of CD-40 signalling	[105]
Piperine	<i>Piper nigrum</i>	Alkaloid	Inhibition of Th2 and mast cell hyperactivity	[9]
Antipyretic compounds				
Acacetin	<i>Potentilla evestita</i>	Flavone	Probably inhibits activity of prostaglandins	[72]
Viscosine	<i>Dodonaea viscosa</i>	Flavonoid	Inhibition of cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2) and microsomal prostaglandin E synthase-1 (mPGES-1)	[61]
16-hydroxy betulinic acid	<i>Mikania cordata</i>	Triterpenoid	Unknown	[84]
6-(3-carboxybut-2-enyl)-7-hydroxycoumarin	<i>Peucedanum ostruthium</i>	Flavonoid	Inhibitor of cyclooxygenase and 5-lipoxygenase activity involved in prostaglandin synthesis	[29]
Linarin	<i>Buddleia cordata</i>	Flavonoid	Unknown	[58]
6-methoxy-7-hydroxy- α -dunnione	<i>Stimmgia canescens</i>	Naphthaquinone	Reduction in lipopolysaccharide-induced fever	[53]
Mangiferin	<i>Mangifera indica</i>	Xanthone	Synthesis of TNF- α is inhibited which acts as a pyrogen	[85]
2-hydroxy-1,4-naphthaquinone	<i>Lawsonia inermis</i>	Naphthaquinone	Unknown	[2]
Usnic Acid and Diffractaic Acid	<i>Usnea diffracta</i>	Dibenzofuran and Sesquiterpene	Unknown	[64]
Artemisinin	<i>Artemisia annua</i>	Polyphenol	Unknown	[63]
Neochlorogenic Acid	<i>Hibiscus sabdariffa</i>	Polyphenol	Inhibition of lipopolysaccharide-induced fever in BV2 microglial cells	[41]
Phenacetin	<i>Bursera grandifolia</i>	Acetamide	Unknown	[91]
Analgesic compounds				
Aspirin	<i>Spiraea ulmaria</i>	Acetylsalicylic acid	Inhibitor of cyclooxygenase 1 and cyclooxygenase 2	[90]
Morphine	<i>Papaver somniferum</i>	Opiate alkaloid	Analgesic effect by binding to mu opioid receptors present in the central and peripheral nervous system cells	[48]
Codeine	<i>Papaver somniferum</i>	Opiate alkaloid	Similar mode of action to morphine. Codeine is metabolised to morphine in animal body.	[8]
Thebaine	<i>Papaver somniferum</i>	Opiate alkaloid	Similar mode of action to morphine. Codeine is metabolised to morphine in animal body.	[42]
Salvinorin A	<i>Salvia divinorum</i>	Diterpenoid	Binds to kappa opioid receptors present in central and peripheral nervous system leading to analgesic effect	[68]
Menthol	<i>Mentha spicata</i>	Terpene	Binds to kappa opioid receptors present in central and peripheral nervous system leading to analgesic effect	[23]
Pawhuskin A	<i>Dalea purpurea</i>	Stillbene	Acts as opioid antagonist and binds selectively to kappa receptors	[28]
Cocaine	<i>Erythroxylum coca</i>	Tropene alkaloid	Acts supraspinally in a dopamine mediated and non-opiate manner to produce analgesic effect	[50]

(continued on next page)

Table 2 (continued)

Compound	Source	Class	Mode of action	Reference
Tetrahydrocannabinol	<i>Cannabis sativa</i>	Cannabinoid	Analgesia by inhibition of release of neurotransmitters and neuropeptides from nerve endings.	[93]
Bronchodilation compounds				
Emodin	<i>Folium Sennae</i>	Anthraquinone	Inhibition of acetylcholine mediated contraction of airway smooth muscle	[71]
Curcumin	<i>Curcuma longa</i>	Polyphenol	Relaxation of tracheal smooth muscles contraction mediated by KCl. Regulation involves calcium channel blocking and potassium channel opening	[22]
Berberine	<i>Berberis aristata</i>	Alkaloid	Inhibition of histamine receptors, cyclooxygenase pathway and nitric oxide which are involved in bronchoconstriction	[75]
9-octadecanamide	<i>Anacardium occidentale</i>	Amide derivative of fatty acid	Inhibition of histamine mediated bronchoconstriction	[5]
Cyclomicrobuxine and its derivatives	<i>Buxus papillosa</i>	Steroidal alkaloids	Inhibition of calcium channels involved in bronchoconstriction	[38]
Citral	<i>Zingiber officinale</i>	Terpenoid	Bronchodilation by regulation of β -adrenergic receptor	[57]
Expectorant compounds				
chlorogenic acid, 3,5-dicaffeoylquinic acid, 3,4-dicaffeoylquinic acid, and 4,5-dicaffeoylquinic acid	<i>Tussilago farfara</i>	Caffeoylquinic acids	Unknown	[100]
Liquiritin apioside, liquiritigenin and liquiritin	<i>Glycyrrhiza uralensis</i>	Flavonoid	Unknown	[44]
Caffeoylquinic acids, astersaponins, and aster peptides	<i>Aster tataricus</i>	Caffeoylquinic acid, saponin and peptide	Unknown	[103]
Imperialine, imperialine- β -N-oxide, isovericine, and isovericine- β -N-oxide	<i>Fritillaria wabuensis</i>	Alkaloids	Unknown	[94]
imperialine, chuanbeinone, verticinone and verticine	<i>Fritillariae cirrhosae</i>	Alkaloids	Unknown	[95]
Vasicine, deoxyvasicine and vasicinone	<i>Peganum harmala</i>	Quinazoline alkaloids	Unknown	[52]

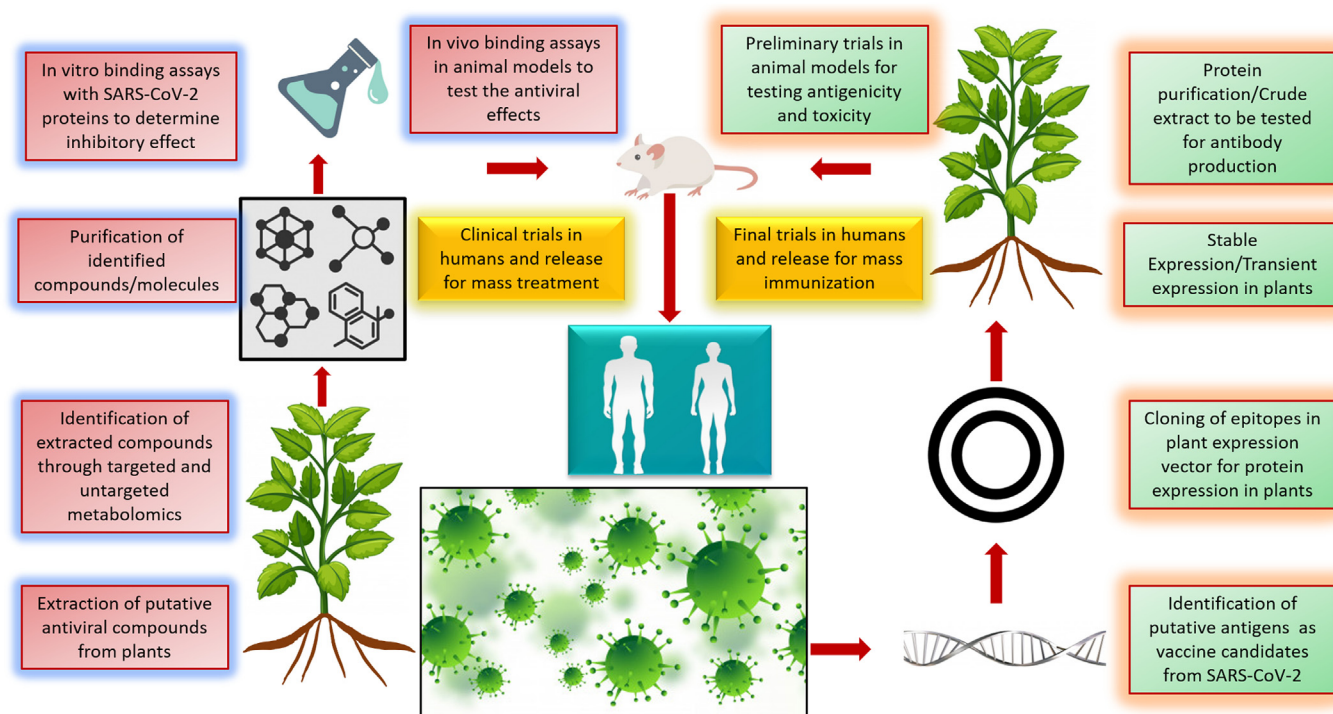


Fig. 2. Different approaches for using plant-based biomolecules against SARS-CoV-2. Plants are a store house of active metabolites, and identification of these metabolites through targeted and untargeted metabolomics is important. These metabolites can be tested for their antiviral activity and released for treating viral diseases. On the other hand, plant based edible vaccines can be synthesized by expressing viral epitopes in plants. These vaccines are easy to store and propagate. (Image created using [freepik.com](https://www.freepik.com)).

at the end-user level.

4. Genetics and genomics approaches for the production of therapeutic biomolecules

4.1. Forward and reverse genetics approaches

Plant biotechnology offers a broad spectrum of production strategies at different levels, including whole plant, tissue, and cell. Hairy roots and cell suspension cultures facilitate the synthesis of biomolecules at large-scale [26]. In addition, advances in genetics and genomics had also facilitated the manipulation of genes and pathways underlying the biosynthesis of therapeutic molecules. Numerous approaches for genetic manipulation of genes and genomes are available in plants, including stable transformation (transgenics and transplastomics), transient and inducible expression systems, gene silencing approaches (knockdown and knockout), and genome editing methods. A transient expression for vaccine production is beneficial over stable transgenics as it saves time and expedites the large-scale manufacturing in pandemic situations. Fig. 2 illustrates how genomics and biotechnology could intervene in producing plant-based drugs. Next-generation sequencing provides comprehensive information about the genes, non-coding regions, and regulatory elements present in the genome, which enables rapid identification of the genes involved in the biosynthesis of therapeutic molecules. Forward genetics approach of estimating the biomolecule content (or large-scale metabolite profiling) in a given population followed by genotyping (genotyping-by-sequencing, double digest restriction-site associated DNA sequencing, whole-genome re-sequencing, etc.) will identify the genomic regions regulating the biosynthesis of individual molecules. These genomic regions (genes/alleles/QTLs) can be effectually used in genomics-assisted breeding for developing elite lines producing higher levels of target molecules. On the other hand, gene cloning enables the isolation and molecular characterization of target genes encoding for active biomolecules that

can be transformed into a different plant system (*Nicotiana*, for example, is a widely used system for plant-based drugs) for the ease of expression, optimization of production and purification. For instance, *N. benthamiana* is now being used as an efficient system for expressing VLP of SARS-CoV-2 to produce a plant-based vaccine. Similarly, these heterologous systems can be used to produce the desired biomolecules that could be isolated and purified for further downstream approaches. A few metabolites could be tissue- or development-specific, and therefore, finetuning their expression throughout the life cycle of the respective plant is imperative to ensure a maximum harvest. For example, β -Eudesmol has been found to have antibacterial and antiviral properties; however, its usage as an antiviral drug is limited due to its low level (2.39%) of production in *Lauris nobilis* [4]. Promoter cloning or manipulation of *cis*-regulatory elements in the promoter regions could provide an amenable solution to this issue. CRISPR/Cas9 approach can be deployed to edit the *cis*-elements present upstream to the gene(s) for ensuring its expression throughout the life cycle of the target plant. Genetic elements regulating post-translational events acting on the therapeutic biomolecule of interest should also be studied.

4.2. Genome editing and overexpression systems

CRISPR/Cas9 method enables precise editing of genes, particularly this applies to knock out the enzymes that utilize the target biomolecule as a precursor for further processing and to facilitate rate-limiting processes for over-production of desired metabolites. Transient approaches, including RNA interference or virus-induced gene silencing, could also assist in finetuning the biosynthetic machinery to achieve a higher level of production. Stable transformation of genes and overexpression in the plant system could be achieved through several approaches existing for genetic transformation. *Agrobacterium*-mediated transformation is one such reliable approach where the gene of interest is cloned into the Ti-plasmid and transferred to a plant for integration into the genome [56]. This approach has been widely used in crop

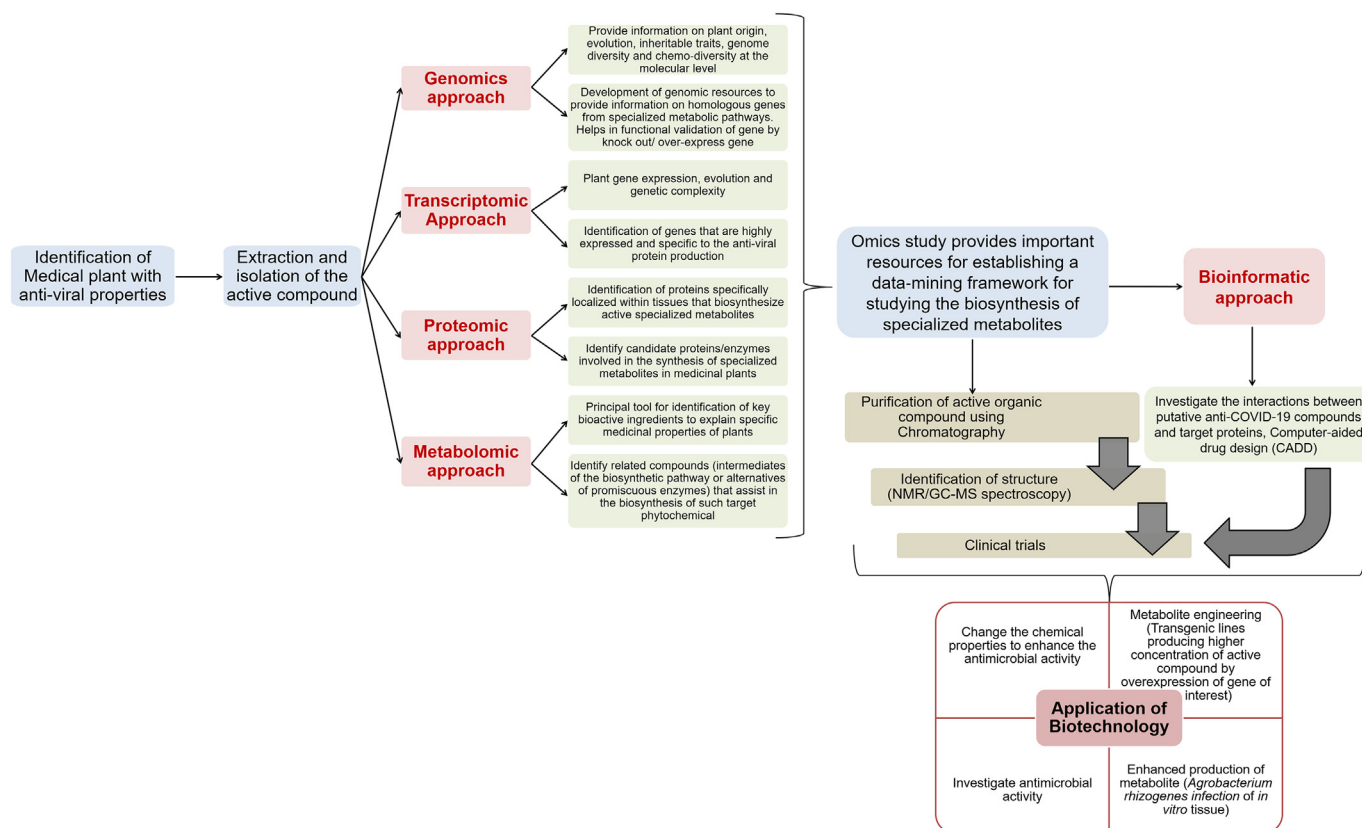


Fig. 3. Schematic representation of biotechnology and omics-based strategies for profiling and application of plant-based antiviral phytochemicals against COVID-19. It includes identification of the plant encoding the active molecule, purification and evaluation for its role against SARS-CoV2. The Omics-based approach helps in recognition of different biological components associated with the pathway of phytochemical synthesis. Initially, Genomic approach is used to detect the gene coding for the active molecule. This information can be used to identify the homologous genes from other plant species and for functional characterization of the gene. The transcriptomic and proteomic approach depicts the active pathways in the plant associated with the molecule production. The metabolomic approach is the primary tool for detecting the main bioactive compound and the biosynthetic pathway regulating its synthesis in the plant. The metabolite or protein identified by integration of these approaches is studied for its role against SARS-CoV2. This is achieved either by computational/bioinformatics-based docking between the active compound and virus encoded proteins followed by clinical trials or by purification of the phytochemical through chromatography followed by its clinical trial. Further, by applying biotechnology the concentration of these metabolites can be increased significantly. It includes developing stable transformations in plants or by expressing the synthesis machinery into a heterologous system or using transformed root cultures or through chemical modifications in the active molecule to increase its potency as an antiviral compound.

improvement for stress tolerance and agronomic traits. Given the broader application, this could be easily adapted for producing target biomolecules in diverse plant systems, where further downstream processing and purification is easy and straightforward. For instance, extracts of Chinese medicinal plants, *Panax ginseng* and *Magnolia officinalis* have anti-inflammatory properties, but since they are endangered species, their use in therapeutics is restricted. In such a case, studying the biosynthetic pathways and engineering them into a model plant species such as maize, tomato, rice, and tobacco reduces the pressure on parent medicinal plants [60] and provides the key to achieve production of beneficial compounds. Some natural compounds may require chemical modifications to increase their potency so that they can be used as a therapeutic drug. For example, a naturally occurring saponin, glycyrrhizin, was found to inhibit the replication of coronavirus, but modifying its glycoside chain enhances the antiviral activity by ten folds [30]. Similarly, increased antiviral activity was observed for tomentins and quercetin-7-rhamnoside as compared to their non-modified precursors [13,14]. These reports accentuate that biotechnology can also bridge the gap between the identification of naturally derived compound(s) and their usage as the therapeutic drug with a reduced timeline and increased efficacy. Also, the administration of plant-based drugs either through topical application or oral intake reduces the stringencies associated with ultra-high purification and storage issues. This will simultaneously reduce manufacturing as well as

downstream processing costs.

5. Conclusions and future perspectives

Plants are primarily under-studied for their use in therapeutic purposes for treating infectious diseases; however, the traditional medicines have taken complete advantage of the entire plant kingdom. The gap between conventional treatment using herbs and extracts and the knowledge on the bioactive compounds present in those plant extracts, as well as their mode of action leading to disease recovery, needs to be bridged. Advances in science and advent of next-generation scientific research and discovery had delivered several tools, techniques, approaches, and strategies that can be effectually used in dissecting the metabolomic profile of plant species to identify the potential compounds that could possess anti-SARS-CoV-2 activities. Computational methods, including molecular modeling, docking, structure analysis, etc. can assist in performing experiments and validation of results virtually before undertaking further *in vitro* and *in vivo* studies. The intervention of genomics and biotechnological approaches to modulate the genes underlying biosynthesis and accumulation of these therapeutic biomolecules gains importance in the current scenario (Fig. 3). The identification of unique compounds present in plants may be laborious, but once identified, screening the compounds for therapeutic applications in treating COVID-19 infected patients, devising

appropriate strategies for optimized production and purification of such compounds, and pursuing further validation studies in the laboratory and clinical trials may be expedited keeping in view the eco-friendliness and safety aspects of plant-based drugs. Also, the availability of a repository of plant-based therapeutic biomolecules will play an important role in confronting future health emergencies.

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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