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Research Paper

Role of Plant Extracts and Plant compounds for COVID-19 Intervention

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ABSTRACT:
Viral infections play a critical role in human disease, and their prevention is a vital issue in safeguarding public health. Despite the advances made in immunization and drug development, preventive vaccines and efficient antiviral therapies are inadequate for COVID-19 virus cure .and also due to the fact of the production viral mutants. Hence establishing an unique antiviral drug for Covid-19 is of great significance and in this direction natural products are an admirable source for such discovery.It is well-known that there are many medicinal plants which have documented advantages to viral infections like COVID-19. This review article will fill in the role some of the most well-known herbs/medicinal plants and various ways to develop them for use.

KEYWORDS: *COVID-19, plant extracts, plant compounds, coronovirus cure*

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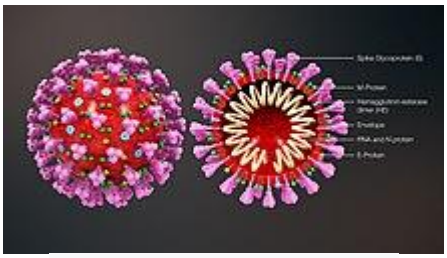
I. INTRODUCTION:



Structural view of a Coronavirus
{Ref: Wikipedia}

Coronaviruses are a group of related viruses that gives rise to [1b] diseases mainly . In humans and gives rise to respiratory tract infections that can have ,mild symptoms like the common cold whereas in other cases COVID-19. can cause death .Symptoms in birds and animals For example in chickens it can cause an upper respiratory tract disease, while in cows and pigs cause diarrhea..A family origin of Coronaviruses establish to the sub-family
Orthocoronavirinae. At pesent it is known that no new effective anti-viral vaccines are available to treat human Coronavirus. All the more this review can establish the fact phytodrugs will play a vital role in the treatment of COVID-19. CoV is an enclosed positive-sense single-stranded RNA. and [1]causing upper respiratory tract and gastrointestinal and mainlycauses in human SARS. which is known [2] human CoV (HCoV) comprises HCoV-229E, -OC43, -NL63, -HKU1.whereas the severe acute respiratory syndrome is known as SARS-CoV . It has already become a global threat with high fatality rate.[3] . Till now the deaths due to COVID-19 stand 3,800,000.worldwide .In 2012, the World Health Organization (WHO) projected a sixth type of HCoV nfection

organized as the Middle East respiratory syndrome coronavirus (MERS-CoV) as having with high fatality rate. It has been reported that about 35% of the global medicine market,estimated to for 1.1 trillion US dollars,have been shared by medicinal plant products from natural plants or herbs.

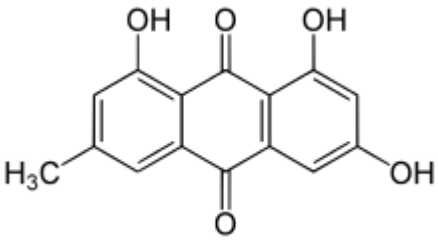
NEED AND PUROSE OF MY REVIEW

Since the emergence of COVID-19 PANDEMIC which has already taken a death toll of ,3,838,375 (updated till June 16,2021) there are only a fewer vaccines available and hence it is the need of the hour is to go for more avenues/resources for COVID-19 cure and this review to some extent will serve the purpose and makes a maiden attempt in this direction This review discusses the role of plant extracts and plant compounds for COVID-19 Intervention, bringing majority of groups in plant chemistry known for anti-covid activity ***under one head***(almost all websites dealing in Covid-19 cure are referred using *Google scholar*) It is my suggestion that Pharmaceutical companies can take up manufacturing these natural compounds for Covid cure (mentioned in the review) due to the following main advantages:

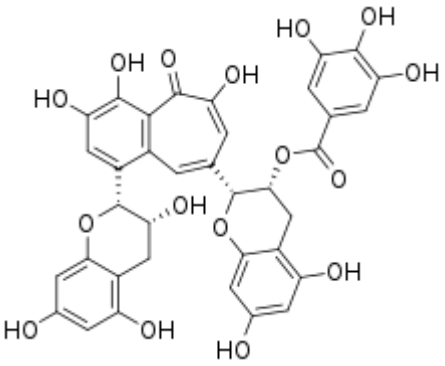
1.Cost effective 2.Having least side effects.

Plant extracts and plant molecules having anti-COVID-19 activity:

In the following paragraphs we describe the medicinal plants/herbs which are known to have anti-coronovirus activity**.** It is reported[5] that emodin, an anthraquinone from *Rheum officinale* {*Polygonaceaee}* obstructed the binding of S protein to ACE2 and decreased the transmissibility of S protein pseudo-typed retrovirus to verocells and adequately choked the interaction between S protein and ACE2 in a dose-dependent manner with IC_{50} of 200 μM, showing it might be a specific therapeutic agent for the treatment of SARS. Chymotrypsin-like protease (3CLPro) of SARS-CoV, an enzyme accountable for proteolysis, is important to coronavirus replication, making it considered as an important target for drug discovery against SARS-CoV. Two natural polyphenols from black tea (*Camellia sinensis* (L.) Kuntze), tannic acid and theaflavin-3-gallate, had the desired advantages.



Emodin



theaflavin-3-gallate

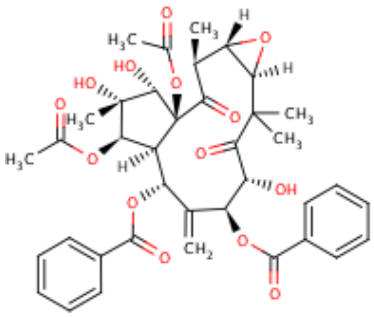
An experimental study described that extracts from *Lycoris radiate*{Amaryllidaceae} *Artemisia annua,*{:Asteraceae} *Pyrrosia lingua*{Polypodiaceae}and *Lindera aggregata* {Lauraceae} show anti–SARS-CoV effect from a lot of chinese herbs. Phytochemicals such as myricetin, scutellarein, and phenolic compounds Isolated from *Isatis indigotica {*Brassicaceae} and *Torreya nucifera{*Taxaceae} play as natural inhibitors against the SARS-CoV enzymes, such as the nsP13 helicase and 3CL protease, .[6,7,8] In addition anti-CoV phytodrugs from the water extract from *Houttuynia cordata* { Saururaceae} reveal antiviral mechanisms against SARS-CoV, such as blocking the viral 3CL protease and countering the viral RNA-dependent RNA polymerase activity.[9]

The molecular simulation study[10] proposes that *Ocimum sanctum Linn{Tulsi}* extract is described as a preventive measure against CoV due to its potential to inhibit response of CoV supported with its immunomodulatory feature and ACE II blocking properties leading to the identification of newer phytodrugs.

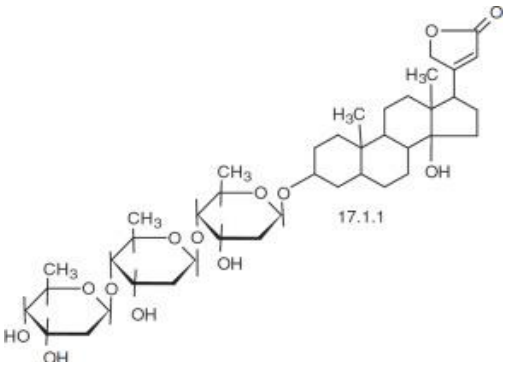
Kansuinine B and Digitoxin:

A study [11] was conducted by Khan to determine phytochemicals for the treatment of COVID-19, focusing on the chemical that has the capacity to bind with Human ACE2 protein as well as with two of the main Sars-Cov-2 proteins which are the the RNA-directed Spike proteins. Two phytochemicals, Kansuinine B isolated from *Euphorbia kansui* {Euphorbiaceae}. (E. Kansui and Digitoxin, extracted from Foxglove seeds

were found to have promising attributes for the treatment of COVID-19. Kansuinine B conceal cytokine response through the expression of the SOCS3 gene.



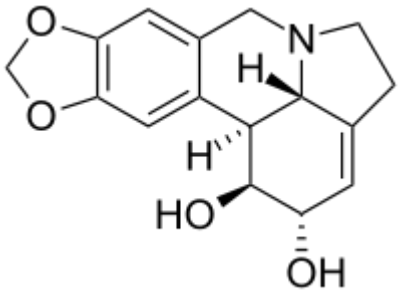
Kansuinine B



Digitoxin

In-silico simulations reveal that both Kansuinine B and Digitoxim have a better affinity and binding properties compared to many other under trial Covid drugs.

The phytochemicals that show promise [12] for the inhibition of coronavirus in humans are scutellarein, silvestrol, tryptanthrin, , caffeic acid, and psoralidin,.Lycorine has been shown to have therapeutic level of antiviral activity. Majority of the polyphenols are described as coronavirus inhibitors.



Lycorine

The mechanism of action [13] of these phytochemicals involves blocking the viruses either during the viral entry inside the host cell or during their duplication . The well-known phytochemicals like flavonoids, terpenoids, lignins, alkaloids, and coumarins have antioxidant activity, and also known to inhibit viral genome. Various plant-derived products have been well studied against viruses like herpes virus, human immunodeficiency virus (HIV), influenza, and hepatitis virus.(**Please refer Table 1 given below**) It is well established that traditional medicinal plants have been continuously as useful medicine for the treatment of various infections. Many well-known flavonoids have been used for treatment of various virus infections. Special attention is being made in the use of terpenoids for their pronounced activity against viral diseases. It can be concluded that antiviral therapies using the phytochemicals for coronovirus are accepted to be less expensive than the allopathic synthetic drugs with very little side reactions A worthful suggestion is to go for . synergistic studies employing phytochemicals in combination with either already FDA-approved drugs to achieve long term anti viral efficacy. The significance of using phytochemicals having antiviral activity can be nanoencapsuled for rbetterdelivery, prolongedaction and hence bioavailability.

Table 1: Complementary and Alternative Medicines that Have Been Studied for Treating Influenza and the Common Cold

Complementary and Alternative Medicines that Have Been Studied for Influenza[1]	Complementary and Alternative Medicines that Have Been Studied for the Common Cold[1]
Chinese herbal medicines	Andrographis (*Andrographis paniculata*)
Dehydroepiandrosterone (DHEA)	Astragalus (*Astragalus membranaceus*)
Echinacea	Chinese herbal medicines
Elderberry	Elderberry (*Sambucus nigra*)
Green tea	Garlic (*Allium sativum*)
N-acetylcysteine (NAC)	Green tea
North American ginseng	Honey
Oscillococcinum	Hydrotherapy
Pomegranate extract	Nasal irrigation
Vitamin C	North American ginseng (*Panax quinquefolius*)
Vitamin D	Vitamin E

3.

Table 1{Ref: Yvette C. Terrie, , Complementary and Alternative Therapies for Colds and Influenza, Pharmacy Times, November 2013 Cough & Cold, Volume 79, Issue 11}

Molecular Docking studies using Natural Compounds for anti-covid activity

The bioactive compounds from Ginger (Zingiber officinale) {Zingiberaceae} are known for their antioxidant, antidiabetic, anticancer, anticoagulant, antiradiation, anti-inflammatory, gastrointestinal, antimicrobial, cardiovascular, anti-obesity, and weight loss effects. An experimental molecular docking showed[14] eight phytochemicals from Alpinia officinarum {Zingiberaceae } and ginger attach with high in silico attraction to closed PLpro conformer and hence can be inferred that they are SARS- CoV-2 PLpro inhibitors and also 8-Gingerol, 10- Gingerol and 6-Gingerol from ginger are potent inhibitors of PLpro, having nM binding affinity and high LE values indicating the compounds from rhizomes of Alpinia officinarum and ginger are shown to bind with the same high affinity.

Maurya utilized[15] molecular docking approach to explore the beneficial roles of phytochemicals and active pharmacological agents present in the following Indian herbs namely Tulsi, Haldi, Giloy, Black pepper, Ginger, Clove, Cardamom, lemon, and Ashwagandha The study was made based on the docking scores calculated by AutoDock Vina, an Improved molecular modeling simulation software, to find out whether these phytochemicals posses notable docking scores to inhibit SARS-CoV-2 infection and other target proteins. Molecular docking studies indicated that, their phytochemical possess anti- inflammatory property and target proteins for prevention and treatment of the COVID19. Molecular docking studies also indicated that, the phytochemicals present in these herbs possess anti- inflammatory property.These target proteins for prevention and treatment of the COVID19. The study showed that many of the phytochemicals of Kadha have significant binding affinity with the main protease. Twelve phytochemicals namely Somniferine A, Tinosporide, Tinocordioside, Orientin, Flavonol glucoside, Withanolide, Apigenin, Cyclocurcumin, Withanolide B, Kaempferol, Withanone and Withaferin A, indicated binding energy lower than the pharmacological inhibitor. . The study showed that an array of the phytochemicals have significant binding affinity with the SARS-CoV-2 spike proteins as well as with host ACE2 protein and furin protein Thus, it is understood that phytochemicals may significantly inhibit viral interaction with the host receptor and slow down or stop the entry of the viral genome inside the host. The spike protein is also known to activate the immune response of the host cell towards CoVs (Li, 2016). The S1 domain of spike acts as a major antigen on the surface of the virus This study indicated that the phytochemicals such as Withanone, Withanolide B, Withanolide, Withaferin A, Ursolic acid, Tinosporaside, Tinocordioside, Stigmasterol, Somniferine A, Quercetin, Oleanolic acid and Crategolic acid have

significant binding energy with nucleocapsid protein The N protein of SARS-CoV are also known to up-regulate the expression of the proinflammatory protein COX2 and also interact with the proteasome subunit p42, which affects a variety of basic cellular processes and inflammatory response. The phytochemicals ,identified may disrupt the formation of RTC and stop the viral genome replication. The study predicts that an array of the phytochemicals such as Withaferin A, Withanolide B, Withanolide, Withanone, Campesterol, Cyclocurcumin,Somniferine A,Stigmasterol, Eriodictyol, Isopiperine, Oleanolic acid, Rhamnetin, Orientin, Quercetin, Piperine, Vicenin etc. found in the preparation of the Kadha, have significant binding affinity with the many of these inflammatory mediators or the molecules involved in this process and concluded that phytochemicals found in the Kadha have significant binding affinity with NIK which can stop NF-κB mediated downstream events.. At the same time, SARS-CoV-2 infection also initiates increased secretion of T-helper-2 (Th2) cytokines (eg, IL4 and IL10) which suppress inflammation. The increased secretion of inflammatory mediators was indicated with moderation of helper T cell responses in COVID19 patients.It can be pointed out that , regular consumption of ayurvedic Kadha in may lower the inflammatory response and upgrade the individual's immunity resulting to reduce the risk of CoVs infection including SARS- CoV-2.

A study [16] was undertaken is to determine if the components of natural origin have an anti-viral effect and which can prevent humans from infection by this coronavirus using the most reliable method is molecular docking, which used to find the interaction between studied molecules and the protein.In this case the basis is on on the inhibitor of Coronavirus (nCoV-2019) main protease. The results of molecular docking showed that among 67 molecules of natural origin, three molecules ,Crocin, Digitoxigenin, and β-Eudesmol are proposed as inhibitors against the coronavirus based on the energy types of interaction between these molecules and studied protein.

It is reported[17] that a high intake of well known phytochemical viz resveratrol may have a protective role, upregulating ACE2, whereas a high intake of dietary fat may have a detrimental role, downregulating ACE2 and on the biological plausibility of cooperations between dietary fat and/or resveratrol and ACE2 gene alterations in the modulation of SARS-CoV-2 illness severity. The results proposed that interactions between ACE2, dietary fat, and SARS-CoV, as well as ACE2, resveratrol, and SARS-CoV influencing illness severity are biologically plausible in humans and hence recommended At the same time, SARS-CoV-2 infection also initiates increased secretion of T-helper-2 (Th2) cytokines (eg, IL4 and IL10) which suppress inflammation. The increased secretion of inflammatory mediators was indicated with moderation of helper T cell responses in COVID19 patients. It can be pointed out that, regular consumption of ayurvedic Kadha in may lower the inflammatory response and upgrade the individual's immunity resulting to reduce the risk of infected by Covid-19.

Flavonoids and its role[18] in treatment of COVID-19 Coronaviruses (CoVs) are an etiologic agent of serious infections in both humans and animals, which can cause disorder not only in the respiratory tract, but also in the digestive tract and in the system. It is well known of the 4 drugs tested (nelfinavir, pitavastatin, perampanel, and praziquantel), nelfinavir was identified as the best potential inhibitor of COVID-19.. Nelfinavir, lopina kaempferol, quercetin, luteolin-7- glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin and epicatechin-gallate had the lowest binding energy and inhibition constants. The affinity of kaempferol bonds is higher compared to other compounds. Hence the study suggested that nelfinavir and lopinavir may represent potential treatment options, and kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7- glucoside, oleuropein, curcumin, catechin and epicatechingallate were the most recommended compounds found in medicinal plants that could act as potential inhibitors of COVID-19 Mpro. .

The following has been reported[19] for the *current methods of new coronavirus treatment*

.A variation of the targets examining the curbing of the RNA transcription, RNA modification, virus packaging enzymes, the capsid, and the surface proteins assist the virus to diffuse into the cells and can be regarded as strategies to deactivate or prohibit the propagation of RNA virus in cells and tissues Currently, studies are focusing on further investigation of the biochemical materials that could inhibit the main proteases of the virus or the compounds that could inhibit the propagation rate of the virus in the cells.. Fortunately, there is a considerable similarity between the SARS-Cov and SARS-Cov2 virus which is more than 80% identity and 96% similarity of the genome . It has been confirmed that the PLPro and 3CLPro of the SARS-Cov and SARS-Cov2 are conserved . Additionally, it is observed that there is a 76.10% identity between the mentioned viruses The above method is applied in this investigation as described here. Based on this similarity, it is expected that the results of the studies about the SARS-Cov could be suggested for the research in the SARS-Cov2 to a high degree. Due to the high similarity19 of the genome and the receptors of SARS-Cov and SARS-Cov2 this study19 suggested possible plant species that might be implicated as anti-SARS-Cov2 agents and also the plants such as U. dioica and S. baicalensis are considered suitable and show relief against COVID-19 disease. Among

the phytochemicals Utrica dioica agglutinin(UDA), an unusual plant lectin and plant secondary metabolites such as glycyrrhizin and baicalin had indicated promising results in SARS-Cov as well as a favorable in-silico results in the COVID19 disease. The use of tobacco plant might be a suitable option as numerous studies demonstrated positive results in production and immunization in-vivo by deployment of the tobacco platform for transformation. and lectins .It is suggested that plant species such as Scutellaria baicalensis (Baikal skullcap), and Utrica dioica (Stinging nettle) as satisfactory candidates for the new coronavirus antiviral research and the use of plants such as Nicotiana tabacum (Tobacco) is reported for the expression of the coronavirus viral antigens due to the efficiency of expression.

In spite of the authorized antimicrobial and immune-boosting potency described[20] for honey,to date there is still a lack of evidence about its potential role amid COVID-19 outbreak. Based on the previously explored antiviral effects and phytochemical components of honey it is reported as an evidence for its role as a potentially effective natural product against COVID-19 Mostly,there are direct and indirect groups of proof shown in the literature referring to the opportunity of honey as a complementary therapy or preventive natural product amid COVID- 19 outbreak and eating honey might help in decreasing the strength of COVID-19 infection either directly based on its potential antiviral effects against SARS-CoV-2, or indirectly across boosting immune responses. The direct and indirect medicinal properties of honey against COVID-19 are mainly related with its content of antioxidant phenolic compounds. In spite of the fact honey benefits anyway , it does not gain by seeking medical consultation and using medications. Further preclinical and clinical investigations are urgently needed to deeply explore the mechanisms of action for honey against COVID-19. A profound and crucial analysis of the pharmacokinetics of phenolic compounds got from honey should also be performed.

Ettayapuram Ramaprasad[21]suggested that preferably available compounds in foods and plants may be one source of anti-viral compounds. Phytochemicals identified from the Nuclei of Bioassays, Ecophysiology and Biosynthesis of Natural Products Database ,were indicated against the main protease (Mpro) of SARSCoV-2,due to its importance in the replication of SARSCoV-2. From Molecular docking studies nine natural compounds were selected for experimental studies ,the plant molecules like carlinoside and quercetin 3-o-sophoroside being the top candidates. Their objective of the study was to screen for natural product chemicals which potentially binds to Mpro. Virtual screening of large number of compounds from Nuclei of Bioassays, Ecophysiology and Biosynthesis of Natural Products Database was carried out using molecular docking and MD simulation. Recently two X-ray crystal structures of Mpro-ligand complexes were disclosed. The RCSB PDB codes were 6LU7 and 6Y2G. 6LU7 and 6Y2G was reported with N-[(5-methylisoxazol-3-yl)carbonyl]alanyl-l-valyl-n~1~-((1R,2Z)-4- (benzyloxy)-4-oxo-1-{[(3R)-2-oxopyrrolidin-3-yl]methyl}but-2-enyl)-l- leucinamide and ~{tert}-butyl ~{N}-[1-[(2~{S})-3-cyclopropyl-1-oxidanylidene-1-[[(2~{S},3~{R})-3-oxidanyl4-oxidanylidene-1-[(3~{S})-2-oxidanylidenepyrrolidin-3-yl]-4-[(phenylmethyl)amino]butan-2-yl]amino]propan-2-yl]-2-oxidanylidene-pyridin-3-yl]carbamate ligands.[5, 6] the relation of both ligands with the with the Mpro catalytic residues, combining Gln166 His4, Cys145 and was supported in molecular docking. Eighteen compounds were selected as initial hits based on the docking score and type of interactions with active site residues. Mpro is one of the potential targets for antiviral treatment against SARS-CoV-2.and hence molecular docking and molecular dynamics simulation techniques were used to screen chemicals from a large natural product database to identify novel inhibitors. Molecular docking and MD simulation displayed nine natural compounds having strong predicted binding affinities for the catalytically important residues of Mpro, with carlinoside and quercetin 3-O-sophoroside being the strongest.

Petric[22]examined antiviral properties (mostly against respiratory viral infections, including coronaviruses by *Echinacea purpurea(F:Asteraceae*). *Echinacea purpurea* preparations proved to be successful as preventive treatment for all coronaviruses, including the newly occurring SARS-CoV2.Experimental results pointed out it could be effective as protective treatment for all CoVs, including newly occurring strains, such as SARS-CoV-211.

Talia Serseg[23] ascertained the discretion of 3CL hydrolase enzyme and showed as a promising therapeutic principle for developing treatments against CoViD-19 and the 3CLpro (Mpro) known for involving in counteracting the host innate immune response and the inhibitory effect of some natural compounds against 3CL hydrolase enzyme was studied, describing the main interactions in inhibitor-enzyme complex. A Molecular docking study was conducted out using Autodock Vina and recognized three candidate agents that inhibit the main protease of corona virus and was found Hispidin, lepidine E, and folic acid bound tightly in the enzyme.

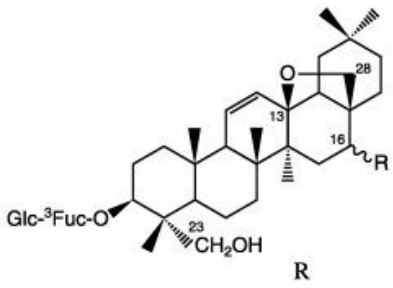
Furnishing a possible therapeutic strategy for CoViD-19, a report [24] indicated that eighteen active substances, including 17 organosulfurcompounds were found in garlic essential oil Using the molecular docking technique, the reserved effect of these compounds on the host receptor angiotensin-converting enzyme 2 (ACE2) protein in the human body that showed to a crucial foundation about coronavirus protection of particular compounds on the main protease (PDB6LU7) protein ofSARS-CoV-2. Seventeen organosulfur compounds, accounting for major contents of the garlic essential oil have powerful reactions with the main

protease and the amino acids of the ACE2 protein PDB6LU7 of SARS-CoV-2. The durable anti-coronavirus activity is considered in allyl disulfide and allyl trisulfide, which account for the highest content in the garlic essential oil. Notably, Docking results indicate the synergistic interactions of the seventeen substances, which exhibit good inhibition of the ACE2 and PDB6LU7 proteins and thus recommending that the garlic essential oil is a valuable natural antivirus source especially for coronavirus.

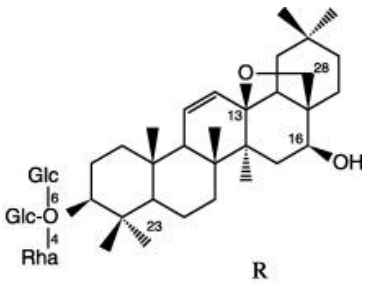
A broad [25] study indicated that Lung-toxin Dispelling Formula No. 1, referred to as Respiratory Detox Shot (RDS), was developed depending on a classical prescription of traditional Chinese medicine (TCM) and the logical appreciation of herbal properties inside TCM. Therapeutic benefits of using RDS for or both disease prevention and control, in an attempt to restrain the coronavirus disease 2019 (COVID 19) had been indicated. RDS performs essentially in the Lung–Large Intestine, Kidney–Urinary Bladder and Stomach–Spleen meridians, with other Zang-fu viscera strategically covered by all nine ingredients. In the context of TCM meridian theory, the multiple components and targets of RDS committed to RDS's dual effects of health-strengthening and pathogen-eliminating. It showed in general therapeutic effects for early COVID-19 control and prevention.

Role of Saiko saponins A,B,C and D in COVID cure:

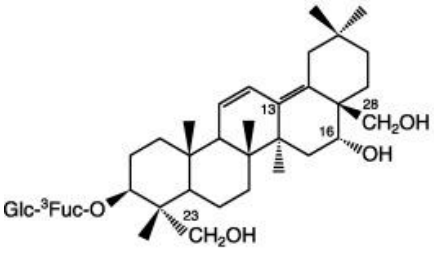
Saikosaponins,extracted from *Radix Bupleuri* {(*Bupleurum Chinense DC*} is a group of oleanane derivatives reported [26] in Chinese medicinal plants and are express for their anti-inflammatory, anti-nephritis, anti-tumor, anti-viral, , anticonvulsant, and hepatoprotective activities. They have anti-coronaviral property by interfering at the early stage of viral replication including absorption and penetration of the virus. Thus, the present study was undertaken to screen and evaluate the potency of different saikosaponins against differentsets of SARS-CoV-2 binding protein *via* computational molecular docking simulations. Docking was proceeded on a Glide module of Schrodinger Maestro 2018-1 MM Share Version on NSP15 (PDB ID: 6W01) and Prefusion 2019-nCoV spike glycoprotein (PDB ID: 6VSB) from SARS-CoV-2. Saikosaponins U and V ,from the binding energy and interaction experimental results, showed the best affinity towards both the proteins proposing them to be prospective research molecule since they point out the intended reaction withNSP15, which is responsible for replication of RNA and also with 2019-nCoV spike glycoprotein which manage the connection with ACE2. It is possible to determine from simulation studies on both proteins, that Saikosaponin U and V have octadecahydropicene ring with substituted oxane ring but one more extra oxane ring of saikosaponin U provide better grip into the widespread binding pocket of spike glycoprotein. The compact structure of Saikosaponin V produces the best suited ligand into the narrow binding pocket of NSP 15. Thus, it can be concluded that Saikosaponin U and V would be the future research interestligand as they mark the desire interaction with NSP15, which is responsible for replication of RNA and also with 2019-nCov spike glycoprotein which manage the connection with ACE2.



Saikosaponin A β--OH
Saikosaponin D α--OH



Saikosaponin C

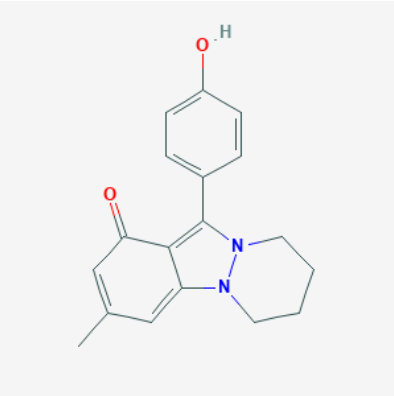


Saikosaponin B_2

Chen [27]identified an unique combination of vitamin C, curcumin and glycyrrhizic acid (VCG Plus) and established to have potential against CoV infection.System biology tools were conducted to develop the potential of potential of VCG Plus in regulating goals and pathways pertinent to inflammation and immune acknowledgements Gene target acquisition, gene ontology and Kyoto encyclopedia of genes and genomes (KEGG) pathway enrichment were carried out consecutively along with network analysis indicating VCG Plus can act on 88 hub targets which are closely connected and associated with immune and inflammatory responses. Specifically, from this study it was suggested that VCG Plus maybe helpful in regulating immune response to fight CoV infections as well as to obstruct enormous inflammatory responses to prevent the onset of cytokine storm. The results suggest that VCG Plus is predicted to be helpful in regulating immune response against CoV infections and inhibiting excessive inflammatory response to prevent the onset of cytokine storm.

Talle[28]searched for plant-based antivirals against the SARS-CoV-2 for promising results as several plants have been shown to possess antiviral activities against beta-coronaviruses (beta-CoVs) aimed to assess bioactive compounds discovered in plants by applying a molecular docking approach to prohibit Main Protease (M^{pro}) (PDB code: 6LU7) and Spike (S) Glycoprotein (PDB code: 6VXX) of SARS-CoV-2.Epigallocatechin gallate, cannabinoids, hesperidine, pectolinarin and rhoifolin had better poses than nelfinavir hydroxychloroquine sulfate and chloroquine as spike glycoprotein prohibitors . Hesperidin, rhoifolin, pectolinarin, and cannabinoids had about the identical pose as nelfinavir. It can be said that these plant compounds have the potential to be developed as specific therapeutic agents against COVID-19 and various natural compounds of plants evaluated in this study showed better binding free-energy compared to nelfinavir, chloroquine and hydroxychloroquine sulfate.

SmarajitMaiti[29] showed that nigellidine, an indazole-alkaloid and key-component of *Nigella Sativa L. {*Ranunculaceae*}(NS;* black-cumin-seed, had been investigated for COVID-19 different protein and TNFα receptorsTNFR1/TNFR2 and IL1R inhibition through molecular-docking study and biochemical-study of cumin seed extract exposure to experimental-rat.



Nigellidine

The NMR, X-ray-crystallographic or Electron-microscopic structures ofCOVID-19 Main-protease(6LU7), Spike-glycoprotein(6vsb), NSP2(QHD43415_2), Nterminus-protenase(QHD43415_3), Nucleocapsid(QHD43423) and Human IL1R (1itb), TNFR1 (1ncf), TNFR2 (3alq) from PDBwere analyzed for receptor-ligand interaction in normal condition and those structures were docked with nigellidine using Autodock-software and Patchdock-server. Where nigellidine indicated highest binding-energy of -7.61 (kcal/mol) and ligand-efficiency value of (-0.35) creating bonds with aminoacids LE1559/ PRO1558/ THR943/LYS945/ ALA1557/MET1556/ LYS945.peak ACE-value of -356.72 was also observed for nigellidine N-terminal-protease reaction Nigellidine also exhibited powerful reaction with NSP2 (-6.28) along with Mpro/3CLpro_Q (-6.38s) Nigellidine manifested closness to TNFR2 (-5.16)TNFR1 (-6.81) and IL1R (-6.23)and TNFR2 (-5.16). In a rat experiment having 2-groups (NS and vehicle processed) of female Wistar-rats were taken for experiments. Nigellidine has hepato/reno-protective;immunomodulatory/anti-inflammatory and antioxidant activities as well as it inhibits important proteins of COVID-19.The above results concluded by molecular modeling that nigellidine can bind in the active sites of specific major proteins of SARS CoV 2, particular host receptors specific for SARS CoV 2, produced inflammatory markers IL1,TNF-α and IL6.

Lyndem using [30] Blind docking technique analysed the interactions between 29 naturally occurring coumarins and SARS-CoV-2 main protease, M^{pro}, out of which 17 coumarins were detected to bind to the active site through the interaction with the catalytic dyad, His41 and Cys145, along with more adjacent residues On correlating the ΔG values of the coumarins bound to the active site of M^{pro}, corymbo coumarin belonging to the class pyranocoumarins, methylgalbanate belonging to the class simple coumarins and heraclenol belonging to the class furanocoumarins, exhibited best binding efficiency and could be considered as potential M^{pro} protease

inhibitors. Preliminary screening of these naturally occurring coumarins as potential SARS-CoV-2 replication inhibitors acts as an step for develop *in vitro* and *in vivo* experimental investigation and analytical validation.

A current study [31]revealed that essential oil components can be associated with key protein targets of the 2019 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and molecular docking analysis was was continued out using one hundred seventy one essential oil ingredients with SARS-CoV-2 main protease (SARS-CoV-2 M^{pro}),SARS-CoV-2 endo-ribonucleoase (SARS-CoV-2 Nsp15/NendoU), SARS-CoV-2 ADP-ribose-1″-phosphataseSARS-CoV-2 RNA-dependent RNA polymerase (SARS-CoV-2 RdRp), (SARS-CoV-2 ADRP), the binding domain of the SARS-CoV-2 spike protein (SARS-CoV-2 rS), and human angiotensin−transforming enzyme names as hACE2. Among these the leading phytochemical with the best normalized docking score to SARS-CoV-2 M^{pro} was the sesquiterpene ,(*E*)-β-farnesene. The best docking ligands for SARS−CoV Nsp15/NendoUwere (*E*,*E*)-α-farnesene, (*E*)-β-farnesene, and (*E*,*E*)−farnesol. (*E*,*E*)−Farnesol displayed the most exothermic docking to SARS-CoV-2 ADRP. It can be inferred that essential oil components may actinteractively essential oils may enhance other antiviral agents, or they may produce some relief ofCOVID-19 symptom.A molecular docking analysis was conducted on 171 essential oil components with the SARS-CoV-2 main protease (SARS-CoV-2 M^{pro}), SARS-CoV-2 endoribonucleoase (SARS-CoV-2Nsp15/NendoU), SARS-CoV-2 ADP-ribose-1″-phosphatase (SARS-CoV-2 ADRP), SARS-CoV-2 RNA-dependent RNA polymerase (SARS-CoV-2 RdRp), the binding domain of the SARS-CoV-2 spike protein (SARS-CoV-2 rS), and human angiotensin-converting enzyme (hACE2). The best docking ligands for theSARS-CoV target proteins were (*E*,*E*)-α-farnesene, (*E*)-β-farnesene, and (*E*,*E*)-farnesol.

Special Note: It is beyond the province of this manuscript to summarize sourcing, CMC, toxicology. etc; hence the interested reader is referred to the book titled as "Dermal Drug Selection and Development-An Industrial Perspective" by Lionel Trottet and Howard Maibach, /Springer link

Conclusion: It is understood that antiviral capacity is well-known for plant extracts and plant molecules . It could be expected that the combination of oriental medicine and western medicine will be helpful in COVID-19 therapeutics. Using herb remedies in the treatment of COVID-19 may be accepted to be passive immunotherapy. However, there have not been much research work on mechanism to expose this virus species antigens. Although the margin of safety of herbal medicine using plant extracts and plant molecules is enormous , more studies need to be elucidated the clear value of using plant extracts and plant molecules to improve physical heath and immune system.

Conflicts of Interest: The authors declare no conflict of interest

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