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Phytochemicals in the Inhibition of COVID-19: A Systematic Review

Dr. Annapoorna S

Assistant Professor, Department of Kayachikitsa, SDM Institute of Ayurveda and Hospital, Bengaluru, Affiliated to RGUHS, Bengaluru, Karnataka, India

ABSTRACT

Ayurvedic medicines has benefits as adjuvant or main-stream therapy in the treatment of COVID-19. This study identifies and recommends the evidence-based herbs to aid the development of successful herbal products against COVID-19 and their variants.

Aims This review article aims to systematically review existing articles on drug research in Ayurveda from AYUSH Research portal

Method A search in AYUSH Research portal was conducted to retrieve studies conducted from January 2020 to December 2021. Using Inclusion criteria, we selected both *in silico* and *in vitro* studies that described the role of phytocompounds in ameliorating COVID-19.

Results and conclusion Majority of the articles have focused on phytochemicals from *W.somnifera* targeting main protease of SARS-CoV-2. The study method in all the articles is molecular docking and molecular dynamics. The experimental evidence for the prediction is very rare. The mean molecular docking scores of phytochemicals is -5.9 Kcal/mol which is like the control values. In conclusion, there is a need to explore phytochemicals from other plants with experimental evidence such that the studies can aid lead identification.

KEYWORDS: *COVID-19, Ayurveda, Phytochemicals, Drug Discovery, AYUSH*

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INTRODUCTION

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) is a global concern due to its high penetrance. The first outbreak of this virus was in Wuhan, Hubei province in China in December 2019[1]. According to World Health Organization, there are 263 million cases of COVID-19 globally as of 3rd December 2021. In India alone, there are 34 million cases were reported[2]. SARS-CoV-2 belong to a group of RNA viruses from coronaviridae family and genus betacoronavirus, that infects humans and avian[3]. The transmission of the virus occurs through contact. The signs and symptoms of the disease are tiredness, cough, fever, dyspnoea, headache, diarrhea. Other complications may include organ failure, pneumonia etc[4].

Currently, agents such as antiviral drugs like chloroquine, hydroxychloroquine, favipiravir; anti-inflammatory drugs like corticosteroids, monoclonal antibodies and vaccines are being used and evaluated[5]. However, these interventions aim at most efficacious management regimen[6]. Hence, there is growing research towards identification of other drugs and agents for the effective treatment of the disease. In this light, traditional system of medicineslike Ayurveda provides a plethora of opportunities. It is reported that about 25% of the modern medicines used in the world are either directly or indirectly originated from plant source. In addition, annual global market price stands at 1.1 trillion US dollars[7]. The data demonstrates that the application of plants in drug discovery is tremendous. In addition, Indian subcontinent is an abode for more than 18000 flowering plant species and is one of the 17 mega biodiversity countries[8]. There are about 2500 plant species recorded in Ayurveda in the treatment of various maladies[9]. Following the rich heritage, Indian AYUSH ministry has published an advisory report as a preventive measure to combat the pandemic[10] and

attempted to bring the traditional medicine system at global stage. Also, the ministry has a repository [https://ayushportal.nic.in/Covid.aspx] that is specific to COVID-19 to disseminate knowledge and promote research. The AYUSH research portal is a national repository consisting of 23868 entries for Ayurveda, 1425 entries for Yoga and Naturopathy, 2691 entries for Unani, 2894 entries for Homeopathy. The articles deposited in the portal is classified into fundamental research, drug research, preclinical and clinical research. Further the entries are categorizedbased on different ailments. It has a distinct link for COVID-19 related entries.

In this review, COVID-19 related research articles deposited in the AYUSH portal are extensively studied to open new arena for research with the aim of providing better conceptual lead for drug discovery.

METHODOLOGY

Study Selection

Ayurveda related research is growing at a higher rate. Hence, the available information in this area is plenty. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to perform the systematic review. The repository was searched for Ayurveda related articles that are specific to COVID-19. The inclusion criteria are 1. Studies that fall under are either fundamental research or drug research category. 2. Only research articles were chosen. 3. Articles with either *invitro* or *in silico* experimental details were only considered for this review. The exclusion criteria are 1. Articles related to clinical and preclinical studies. 2. Review, survey, case study articles 3. Non-relevant articles such as mental health, non-herbal interventions, comorbidities were omitted.

Data Extraction

The selected articles were extensively and exhaustively studied to extract data and critically analyzed. In brief, the data from articles were tabulated in a pre-determined spreadsheet. The data included both qualitative and quantitative information. The qualitative information included the reference to the article, phytochemicals under study, target protein. The quantitative data included the docking scores of the phytochemical and protein targets.

RESULTS

Articles selected for the study

In total, 237 relevant articles were retrieved by the search strategy as described in **Figure 1**. Of these, 126 articles were excluded because they were not satisfying the inclusion criteria. Another 97 articles were excluded as the articles were in exclusion criteria. Finally, 14 articles were included in the present study based on the research topic.

Outcome of data extraction

The data collected from articles are summarized in**Table1**. Twelve of the articles were based on *in silico* analysis and two were based on both *in vitro* experiments and *in silico* analysis. The plants involved in the studies were *Azadiracta indica*, *Camellia sinensis*, *Isatisindigotica*, *Momordica charantia*, *Nigella sativa*, *Ocimum sanctum*, *Rhus succedanea*, *Terminalia chebula*, *Tinospora cordifolia*, *WithaniaSomnifera* and *Zingiber officinale*. Majority of the work were done on phytochemicals from *W.somnifera*. Among the significant phytochemicals, 33 of the phytochemicals were targeting main protease of COVID-19. Other targets used are spike protein, NSP15 endoribonuclease and transmembrane protease serine 2. A bar plot in **Figure 2** represents the significant binding scores of phytochemicals against main protease studied in the articles in comparison with a control. The control is the average binding scores of eleven experimentally studied inhibitors of SARS-COV-2 Mpro[11].

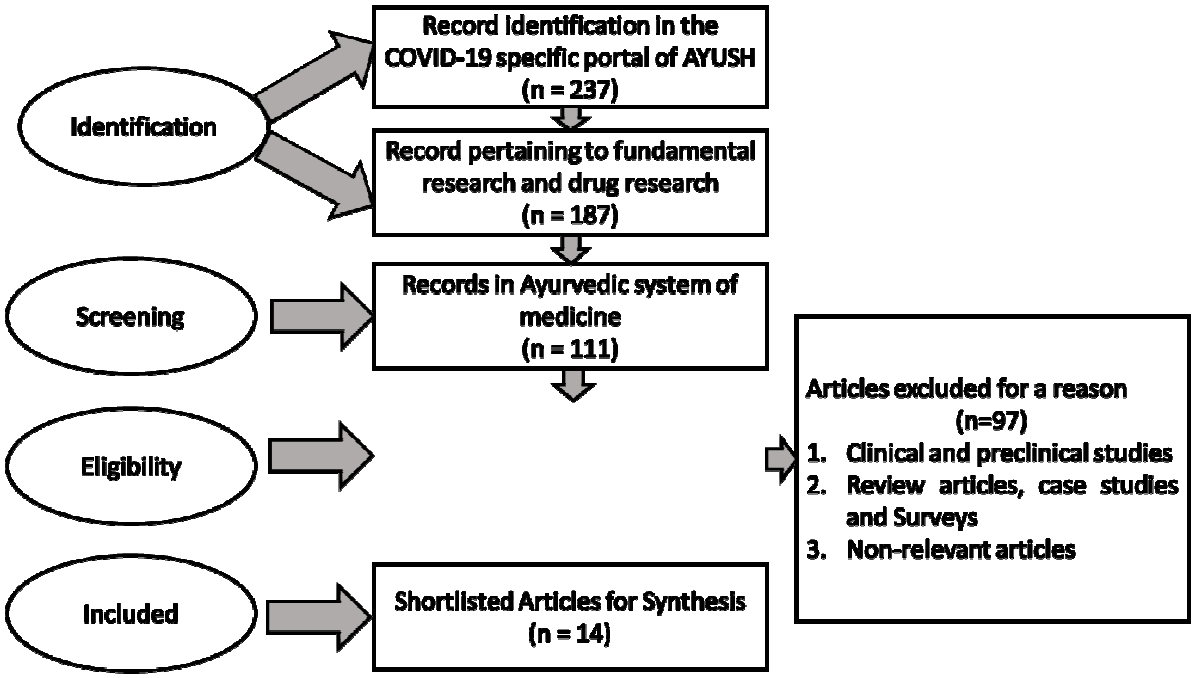

Figure 1 Graphical representation of literature search and selection process

Discussion and Conclusion

This review has focused on COVID-19 related articles in AYUSH portal and has synthesized that majority of the studies in Ayurvedic medicine against COVID-19 virus is done using *W.somnifera*. In addition, it is noteworthy that the studieswere*in silico* based. From the bar plot, it is evident that greater part of the phytochemicals is at par with the control group. However, agathisflavone and amentoflavone showed the lowest binding energy. Upon further analysis, it was observed that this study was conducted using FlexX software, while others were studied using either AutoDOCK Vina or Glide. The scoring functions used in these softwares are different which has led to a sharp change in the binding scores[12].

The negative binding free energies in more favorable in nature because they promote binding to occur with ease. In the review, we have noted that phytochemicals ursolic acid, somniferone, tinocordiside, vicenin and isorientin 40-O-glucoside are shown to have positive binding energies. This indicates that external energy is needed for the ligand-protein interaction to occur. Hence one must consider these situations while progressing with lead identification. In conclusion, the review has identified the potential of *in silico* studies in decipher protein-ligand interactions. However, the author opines that these data require experimental validation. In addition, this article points out that many of the other medicinal plants and phytochemicals remain unexplored. Thus, Ayurvedic medicines/medicinal plants offer huge opportunities for further lead identification.

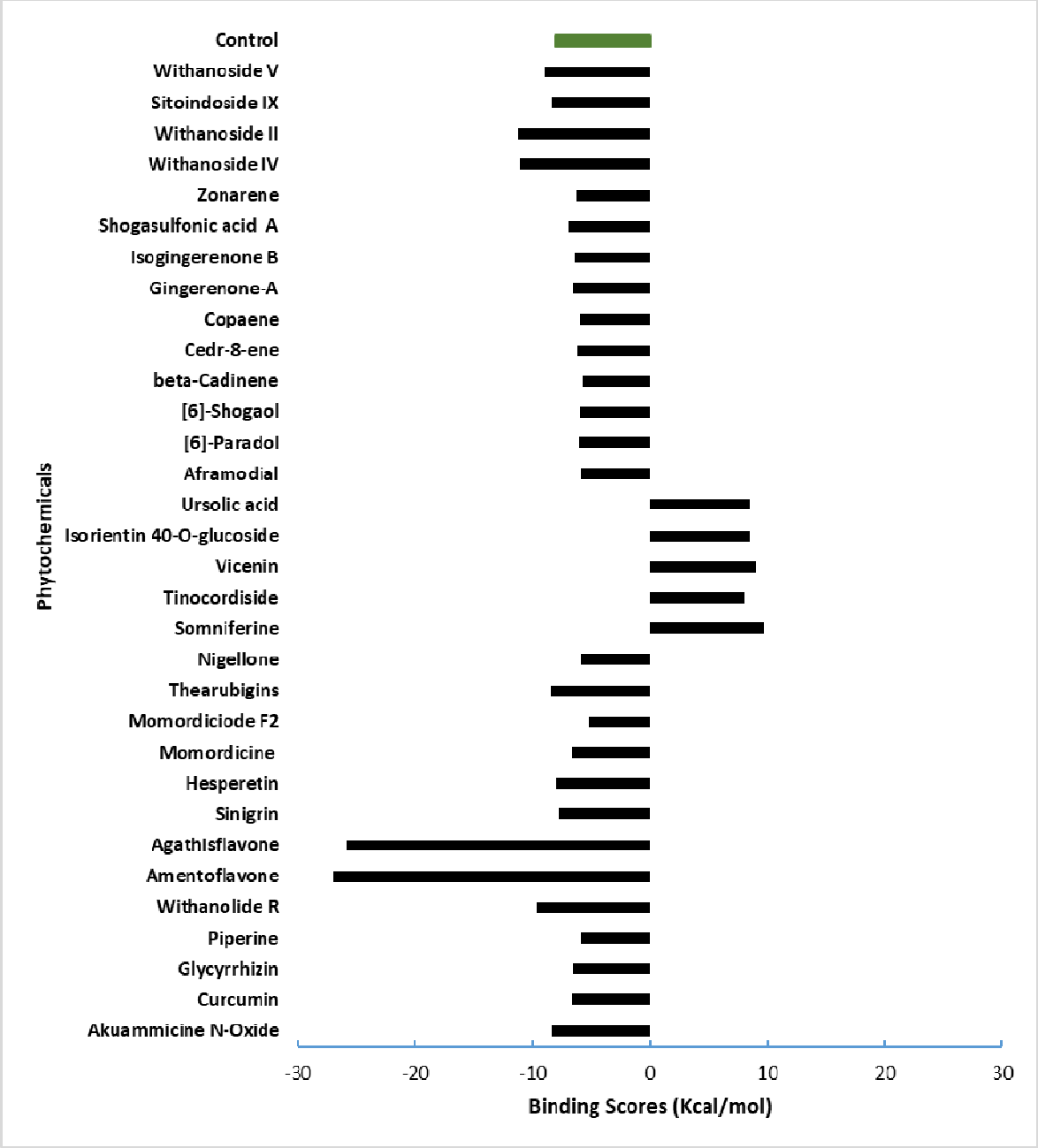

Figure 2 A bar plot of binding scores of phytochemicals against main protease.(Control is the average of binding scores of experimentally tested inhibitors of main protease [11])

Type of study	Plants/Phytochemical under study	Study design	Experimental outcome	Target Protein	References
In silico	***Withaniasomnifera***[Tropine, Ashwagandhanolide, Quercetin-3-O-galactosyl-rhamnosyl-glucoside, Dihydrowithaferin A, Withanoside IV, Withanolide N, Withanolide N, Withanoside III, Withanoside XI, Hydroxychloroquine, Anaferine, Quercetin, Withanoside V, Withasomnine, Pelletierine_Isopelletierine, Tropine]	Molecular Docking and Dynamics Studies	Quercetin-3-O-galactosyl-rhamnosyl-glucoside binds to NSP15 endoribonuclease (-6.70 Kcal/mol) and receptor binding domain of prefusion spike protein (-9.25 Kcal/mol)	NSP15 endoribonuclease (PDBID: 6W01) and receptor binding domain of prefusion spike protein (PDBID:6M0J)	[13]

In silico	**AYUSH-64**[Nb-Demethylalstogustine_N_oxide, Gentiopicroside, Vanillic acid, Ursolic acid, Picroside I, Echitamine, Swerchirin, Methylbellidifolin, Gentiopicrin, Picroside II, Picroside IV, Acetovanillone, Apocynin, N(4)-demethylalstogustine, Pikuroside, Kutkoside, Sweroside, AMarogentin, Oleanolic acid, Acetoxybonducellpin C, 2-Acetoxycaesaldekarine, 14(17)-Dehydrocaesalpin F, Caesaldekarine, Caesalmin B, 2-Acetoxy-3-deacetoxycaesaldekarin E, Norcaesalpinin C, Norcaesalpinin B, Norcaesalpinin A, 17-Norbonducellpin C, 3-O-Acetylnorcaesalpinin A, Caesalpinin F, Caesalpinin E, Caesalpinin D, Caesalpinin C, Caesalpinin G, Echitamidine N-oxide, Ochitaminic acid, akuammiginone, Akummicine N-Oxide]	Molecular Docking and Dynamics Studies	Akuammicine N-Oxide in AYUSH-64 showed best binding energy of -8.4 kcal/mol with Main protease. MD simulation showed that the protein-ligand complex was stable	Main Protease (Mpro; PDB ID: 6LU7)	[14]
In silico	Azadiractin, Beta_Sitosterol, Curcumin, Gingerol, Glycyrrhizin, Piperine, Quercitin, Thymoquinone, Ursolic Acid	Molecular Docking	Curcumin, Glycyrrhizin and piperine showed good binding against protein with -6.6, -6.5 and -5.9 Kcal/mol binding energy	Main Protease (Mpro; PDB ID: 6LU7)	[15]
In silico	**FDA Approved Alkaloids** [Colchicine, Codeine, Piperine, Papaverine, Ergometrine, Theophylline, Theobromine, Caffeine]	Molecular Docking	"Papaverine binds to 5R7Y (-19.28 Kcal/mol); 5R7Z (-23.16 Kcal/mol); 5R80 (-16.80 Kcal/mol); 5R81 (-18.55 Kcal/mol); 5R82 (-14.11 Kcal/mol) and Ergometrine showed 5R7Y (-18.01 Kcal/mol); 5R7Z (-16.21 Kcal/mol); 5R80 (-24.74 Kcal/mol); 5R81	Protease (PDBID: 5R7Y, 5R7Z, 5R80, 5R81 and 5R82)	[16]

			(-20.48 Kcal/mol); 5R82 (-4.79 Kcal/mol) binding scores		
In silico	***Withaniasomnifera*** and ***Azadirachta indica*** [27-Deoxy-14-hydroxywithaferin A, Nimolicinol, 17-Hydroxywithaferin, Withanolide R, 27-Hydroxywithanone, 12-Deoxywithastramonolide, 27-Deoxywithaferin A, 2,3-Dihydrowithaferin A]	Molecular Docking and Dynamics Studies	Withanolide R showed highest binding energy (-9.63 Kcal/mol) was showed by aginst Main Protease and 2,3-Dihydrowithaferin A (-7.45 Kcal/mol) showed highest binding energy against spike protein	Main protease NSP5 (PDB ID: 6LU7) and Spike protein (PDB ID: 6LZB, chain B)	[17]
In silico	***Rhus succedanea*** [Amentoflavone, Agathisflavone, Robustaflavone, Hinokiflavone, Rhusflavanone, and Succedaneaflavanone]	Molecular Docking and Dynamics Studies	Amentoflavone (-27.04 kcal/ mol) and Agathisflavone (-25.87 kcal/mol) interact strongly with the catalytic residues	Main Protease (Mpro; PDB ID: 6LU7)	[18]
In silico	***Isatisindigotica*** [Indigo, Indirubin, Indican, Sinigrin, Quercetin, Naringenin, beta-sitosterol, Aloeemodin, Hesperetin, Daidzein, Emodin, Chrysophanol]	Molecular Docking and Dynamics Studies	Sinigrin (-7.8 Kcal/mol) and hesperetin (-7.9 Kcal/mol)	Main Protease (Mpro; PDB ID: 6LU7)	[19]
In silico	***Momordica charantia L.*** and ***Azadirachta indica*** [Momordicine, Deacetylnimninene, Margolonone, Momordiciode F2, Nimbandol, 17-Hydroxyazadiradione, 17-Hydroxyazadiradione]	Molecular Docking and Dynamics Studies	Momordicine and Momordiciode F2 exhibited good inhibition potential -6.6 Kcal/mol and -5.2 kcal/ mol)	Main Protease (Mpro; PDB ID: 6LU7)	[20]
In silico	***Zingiber officinale*** [(-)-Camphor, (-)-Germacrene_D, (-)-Zingiberene, (+)-Cyclosativene, (E)-Nerolidol, (E,E)-alpha-Farnesene, (S)-6-Gingerol, [6]-Gingerdione, [6]-Paradol, [6]-Shogaol, [7]-Paradol, 1,8-Cineole, 10-Shogaol, 1-Dehydro-[10]-gingerdione, 2-Nonanone, 3-Carene, 4(10)-Thujene, 4-Terpineol, Aframodial, alpha-Muurolene, alpha-Pinene, beta-Bisabolene, beta-Cadinene, beta-Santalol, beta-Sesquiphellandrene, Borneol,	Molecular Docking	Aframodial (-5.9 Kcal/mol), [6]-Paradol (-6.1 Kcal/mol), [6]-Shogaol (-6.0 Kcal/mol), beta-Cadinene (-5.8 Kcal/mol), Cedr-8-ene (-6.2 Kcal/mol), Copaene (-6.0 Kcal/mol), Gingerenone-A (-6.5 Kcal/mol), Isogingerenone B (-6.4 Kcal/mol),	Main Protease (Mpro; PDB ID: 6LU7)	[21]

	Cedr-8-ene, Citronellol, Copaene, Geraniol, Gingerenone_A, Isogingerenone_B, Nerol, Nonanol, Sesquithujene, Shogasulfonic_acid_A, Terpinolene, Zingiberenol, Zonarene, Safrole]		Shogasulfonic acid (-6.9 Kcal/mol) A and Zonarene (-6.3 Kcal/mol)		
In silico	***Withaniasomnifera*** [17alpha-hydroxywithanolide D, 2,3-Dehydrosomnifericin, 24-25-dihydrowithanolide D, 27-Deoxy-14-hydroxywithaferin A, 27-Deoxywithaferin A, 27-Hydroxywithanolide B, Anaferine, Ashwagandhanolide, beta-amyrin, Scopoletin, SitoindosideiX, Somniferine, Somnifericin, Withaferin A, Withanolide A-G,J,L-S, Withanone, Withanoside II-V,VIII,X,XI, Withasomnine]	Molecular Docking and Dynamics Studies	Withanoside II (-11.30 Kcal/mol), Withanoside IV (-11.02 Kcal/mol), Withanoside V (-8.96 Kcal/mol) and Sitoindoside IX (-8.37 Kcal/mol) exhibited the highest docking energy. MD simulation study of 100 ns predicts Withanoside V possess strong binding affinity and hydrogen-bonding interactions with the protein active site and indicates its stability in the active site	Main Protease (Mpro; PDB ID: 6LU7)	[22]
In silico	***Tinospora cordifolia*** [20 β-hydroxyecdysone, Aporphine, Arabinogalactan, Berberine, Bergenin, Chasmanthin, Choline, Columbin, Cordioside, Ecdysterone, Heptacosanol, Isocolumbin, Jatrorrhizine, Magnoflorine, Octacosanol, Palmarin, Palmatine, Pregnane glycoside, Sinapic acid, Syringin, Tembetarine, Tetrahydropalmatine, Tinocordifolin, Tinocordioside, Tinocordiside, Tinosponone, Tinosporin, Beta-sitosterol], ***Ocimum sanctum*** [3-carene, 4-hydroxybenzaldehyde, 4-hydroxybenzoic acid, Aesculin, Alpha-Cadinol, Ascorbic acid, Bergamotene, Cadinene, Carvacrol, Caryophyllene, Chlorogenic acid, Cirsilineol,	Molecular Docking	Withanoside V(10.32 kcal/mol) and Somniferine (9.62 kcal/mol) from *Withaniasonmifera*; Tinocordiside (8.10 kcal/mol) from *Tinospora cordifolia* and Vicenin (8.97 kcal/mol), Isorientin 40-O-glucoside 200-O-p-hydroxy-benzoagte (8.55 kcal/mol) and Ursolic acid (8.52 kcal/mol) from *Ocimum sanctum* showed good binding scores	Main Protease (Mpro; PDB ID: 6LU7)	[23]

	Cirsimaritin, Citral, Estragole, Eucalyptol, Eugenol, Gallic acid, Gallic acid ethyl ester, Gallic acid methyl ester, Galuteolin, Isorientin, Isothymonin, Isothymusin, Isovitexin, Linoleic acid, Linolenic acid, Luteolin, Luteolin-7-O-glucuronide, Methyl cinnamate, Methyl eugenol, Methylchavicol, Molludistin, Ocimene, Oleic acid, Rosmarinic acid, Sitosterol, Stearic acid, Terpinene-4-ol, Ursolic acid, Vanillic acid, Vicenin, Vicenin-2, Vitexin, Aplha-pinene, Beta-pinene] and ***Withaniasomnifera*** [Anaferine, Anahygrine, Chlorogenic acid, Choline, Cuscohygrine, Ergostane, Hentriacontane, Hygrine, Isopelletierine, Pseudotropine, Scopoletin, Somniferine, Tropanol, Tropine, Withanolide D,G,J,N-R Withanoside II-VI, 3-b-hydroxy-2,3-dihydrowithanolide F]				
In silico	***Nigella sativa*** (Carvacrol, Nigellone [Dithymoquinone,Nigellicine, Nigellidine, Nigellimine, Thymohydroquinone, Thymol, Thymoquinonone]	Molecular Docking and Dynamics Studies	Nigellone have shown the most significant inhibitory potential with binding energy of -5.48, -5.89, -7.14 and -6.97 Kcal/mol against all 4 protein targets	Prefusion 2019-nCoV spike glycoprotein(PDBID: 6VSB); Main Protease (Mpro; PDB ID: 6LU7); SARS-CoV-2 spike glycoprotein (PDBID: 6VXX) and SARS- CoV-2 chimeric receptor-binding domain complexed with its receptor human ACE2 (PDBID:6VW1)	[24]
In silico and *In vitro*	***Camellia sinensis*** and ***Terminalia chebula*** [Thearubigin, quercetin-3-O-rutinoside, Hesperidin]	Experimental study and Molecular Docking	Thearubigins binds to main protease with a binding energy of −8.53 kcal/mol	Main Protease (Mpro; PDB ID: 6LU7)	[25]
In silico	Withaferin-A, Withanone and caffeic acid phenethyl ester	Molecular Docking and	Withaferin-N showed stronger binding (-4.30	Homology-based structural model of transmembrane	[26]

and *In vitro*		Dynamics Studies; MCF7 cells expressing TMPRSS 2	Kcal/mol) to TMPRSS2 and the MCF2 cells treated with withaferin-N showed downregulation of TMPRSS2	protease serine 2 (TMPRSS2), a cell surface receptor	

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Declaration of conflict of Interest
No conflict of interest

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