Original Article

The Prospective Use Of Phytochemicals Against Covid-19: A Review

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Abstract

The unpredictable global pandemic faced by the world in 2019, recognised as COVID-19, originated by SARS-CoV-2 virus has threatened human wellbeing and public safety across the entire world, by affecting more than six hundred million people as well as more than 6.7 million global deaths, as of January, 2023. This worldwide epidemic drew the attention towards the necessity of effectual defensive and curative processes in order to extend anti-viral treatment against the deadly virus. Many phytochemical constituents have been recognized to have a variety of curative characteristics against various viral diseases and thus it is becoming the need of the hour for the research community to attempt for anti-viral drugs from phytochemicals that can strengthen our immune system in order to combat COVID-19. Through this review article, we have attempted to analyse the prospective anti-viral implications of few phytochemicals, viz., quercetin, thymoquinone, caffeic acid, rosmarinic acid, ursolic acid, vanillin, thymol, ellagic acid etc., against the SARS-CoV-2.

Keyword: Coronaviruses, COVID-19, SARS-CoV-2, Anti-viral, Phytochemicals.

INTRODUCTION

Coronaviruses have been recognised to be an assemblage of viruses that instigate mild to severe respiratory diseases in animals as well as in humans. The life-threatening COVID-19, a widespread strain of coronavirus caused by SARS-CoV-2 or severe acute respiratory syndrome coronavirus-2, first broke out in November 2019, in the Wuhan city, China [1, 2] and World Health Organization reported its first case on December 31, 2019 [3]. Attributable to its unbelievably extreme transmissibility, this disease extended all over the world with exceptional swiftness in a very short period and World Health Organization classified this outburst as a pandemic, Public Health Emergency of International Concern on March 11, 2020 [3-5]. It has affected a total of 229 countries and territories across the world. Investigations done using purification and sequencing analysis using bronchoalveolar lavage fluid samples, it was reported to be strongly correlated to two bat-derived SARS-like coronaviruses and severe acute respiratory syndrome coronavirus, known as SARS-CoV and Middle East respiratory syndrome coronavirus, known as MERS-CoV [6]. It overpoweringly surpassed MERS-CoV as well as SARS-CoV, which caused lethal respiratory diseases in humans in 2012 and 2002, not only in terms of the rapid rising in number of cases recorded, but also in the spatial variety of outbreak regions. In this day and age, COVID-19 has manifested itself in the history to be the third most pathogenic human coronavirus outbreak among the human populace of this century. Although, it is reported to be less fatal compared to SARS and MERS, its rapid and extreme transmissibility caused the severest danger to human health in this century in the entire world. This emerging health catastrophe has posed a thorny period all over the globe, obstructing usual lifestyle of people, and to deal with the unexpected situations, governments of several countries, had to issue lockdowns [7-9].

The scientific research community across the globe has reported quite an assortment of analyses on COVID-19 with an aim to potentially diminish the load of this rising health crisis, regrettably, till this date even, no medicines or vaccines have been proven to be able to provide complete prevention and cure of the virus. The vaccines used were not successful in providing complete prevention as there have been numerous numbers of cases reported after vaccination, and even deaths, and also, these vaccines were reported to have many side effects. We all know that, the improvement of novel curative agents, as well as vaccines is an expensive and most importantly, a time-consuming process with high chances of failure, as well [11, 12]. And to add above them all, the reported cases and situations faced by different countries have also confirmed the fact about SARS-CoV-2 that, as it has been evolving, it is constantly altering and adopting itself with a number of mutations which led to a number of prominent variants, including Alpha, Beta, Delta and Omicron. These variants further went through mutations to form branches of themselves, leading to sub-variants. For instance, the deadly Delta variant has up to 200 sub-variants. Recent news from China, as well as per the reports of WHO, China is currently witnessing an unprecedented COVID-19 surge due to the outbreak of a new highly transmissible Omicron sub-variant BF.7 [13, 14]. Although these new variants have been expected as a part of the evolution of viruses, however, timely monitoring and dealing with them is becoming a challenge for the world for human survival. Furthermore, the

nonexistence of specific medicine or precise curative procedure for COVID-19 pushed the researchers in the entire world, to investigate other potential alternatives for effective tackling of the virus.
Manifesting all these existing unpredictable circumstances, it is becoming imperative to think about diverse approaches in order to deal with the infections related to different variants of the virus. Starting from the prehistoric period to this modern age, various plants containing different phytochemicals, which have medicinal or therapeutic benefits, have been proven to be outstanding, well-acknowledged, safer, inexpensive, non-hazardous and suitable substitute of conventional medicines in case of various infectious diseases [15-21]. Quite a number of recent reports have indicated the prospective ability of different plant polyphenolic compounds and alkaloids in the prevention and cure of COVID-19. With an aim to extend efficient COVID-19 treatment, preliminary investigations include such compounds, which are FDA-recognised or known to be suitable, secure and harmless in case of therapeutic utilization [22].

These plant derived phytochemicals, such as polyphenols, flavonoids, alkaloids etc., have been considered to be of extreme importance by the modern research community, concerned with medicinal, biological, health or pharmaceutical sciences,attributable to their broad spectrum of health benefits, like antioxidant, antitumor, anti-cancer, anti-mutagenic, anti- fungal, anti-bacterial, neuroprotective, anti-viral, anti-inflammatory, anti-pathogenic, cardioprotective activity, etc. [23- 27]. Many relevant studies have revealed that these polyphenolic compounds contain manifold indispensable features against viral infections like repression of viral imitation [28], modification of immune system [29], viral uptake reduction [30] etc., and also have proven to be successful against various viruses like, HIV, Japanese encephalitis, rabies, chandipura virus, influenza viruses, enterovirus, coronaviruses, etc., [15, 31-33]. In this review, we aim to recapitulate the curative prospects of some vital phytochemicals against this historically lethal infection of this century that has intimidated the human wellbeing across the globe.

METHODOLOGY

The literatures for this short review were extracted from various research and review articles by searching in the scientific literature databases that includes PubMed, Scopus, Scope Med, Web of Science, Google Scholar, and Science direct using different keywords like - coronavirus, COVID-19, SARS-CoV-2, anti-viral, phytochemicals, natural products, phenolic compounds, etc.

RESULTS AND DISCUSSIONS

From the wide range of the literatures studied and analysed for this review, some of the naturally occurring polyphenolic compounds or phytochemicals that were reported by various scientists to be successful in inhibiting the SARS-CoV-2 virus and thus depicted potential ability as preventive or curative herbal medicines or thought to be prospective candidates for drug synthetic purposes of COVID-19 infections are summarised below-

Quercetin is polyphenolic component that belongs to a set of plant pigments, well recognised as flavonoids. It is a pentahydroxyflavone containingfive hydroxyl groups at the 3-, 3'-, 4'-, 5- and 7- positions, named (3,3′,4′5,7-pentahydroxyflavone), and it exist in a variety of plants and foods, such as berries, apples, plum, radicchio, grape, watercress, onions, capers, green tea, red wine, etc. Ithas a wide range of therapeutic potentials, counting cardio-protective, antioxidant, antiallergic, anti-inflammatory, anticarcinogenic, antibacterial, antiviral, antihypertension and immunomodulatory activity [34-39]. Its capacity against coronavirus infections were investigated using different variants of the virus [40] and it was observed that its hydroxyl group controls the inhibition of the viral 3-chymotrypsin-like cysteine protease ($3CL^{pro}$), which plays fundamental role inthe replication and polyprotein processing of the virus and is indispensable for the virus life cycle. Molecular modelling and Q189A mutation experiments have recognised Gln189 to be of extreme importance for binding of quercetin. Also, its administration with Vero E6 cells can disrupt viral entrance depicting an EC_{50} of 83.4 μM and small CC_{50} of 3.32 mM[40]. It can also bind and hinder the proteolytic action of 3CL protease of the virus demonstrating an IC_{50} of 4.95 μM [41].

The flowering plant *Nigella sativa* consists of various bioactive components including thymoquinone, α-hederin, and nigellimine and it is found to effective in COVID-19 treatment as it blocks the virus entrance to receptor pneumocytes via ionophore supply that improves zinc intake, thereby improving the receptors immunity against SARS-CoV-2 and additionally restraining the replication of the virus [42]. A molecular docking experiment acknowledged nigellidine and α-hederin to be effective against SARS-CoV-2 [43]. It was found that the positive impacts of thymoquinone might possibly be augmented by means of a supplemental zinc salt as it may improve natural and adaptive immunity during life-threatening viral or bacterial diseases, and also, intake of zinc salt supplement along with thymoquinone may have superior benefits as thymoquinone acts as an ionophore that allows the penetration of the ion through pneumocytes, whichare the target cells of the virus [44]. Thus, these phytochemical constituents of *Nigella sativa* seeds could be prospectiveherbal medicine for the treatment of COVID-19 [45].

Ursolic acid, also known as urson, prunol, malol or 3-β-hydroxy-urs-12-en-28-oic acid, is a pentacyclic lipophilic triterpenoid, found in the epicuticular waxes of apples and particularly profuse in apple peels, rosemary, thyme, lavender, bilberries, peppermint, elder flower, oregano, hawthorn, prunes, cranberries, holy-flower, etc., and can also be obtained from medicinal plants like- *Ilex paraguarieni, Mirabilis jalapa, Mimusops caffra* and *Glechoma hederacea*, etc. It has depicted a variety of therapeutic benefits like, neuro-protective, antioxidant, cardio-protective, anti-inflammatory, serum

lipid-lowering, antibacterial, antineoplastic, anticarcinogenic, antihepatotoxic, and anti-diabetic potential, etc. [46-54]. *Tegen et al.*, recommended that plants, containing various components with anti-viral ability like ursolic acid may have

prospective potential to be effective against SARS-CoV-2 [55]. Ursolic acid has been found to be effectual against SARS-CoV-2 as it effectively binds and thus blocks the SARS-CoV-2 main proteinase (M^{pro}), the key cysteine protease of coronavirus-2 that mediates the viral replication and transcription. It is reported to be a prospective inhibitor of M^{pro} [56]; and also, molecular docking and molecular dynamic simulation studies indicated that three ligand molecules interacts and get attached to the M^{pro} during the optimum time of 50 nanoseconds of molecular dynamics (MD) simulations [57]. Among all the tested compounds, ursolic acid exhibited maximum docking score with the M^{pro} of coronavirus-2, with a binding energy around 8.7 kcal/mol. It also depicted highest docking score for the papain-like protease (PL^{pro}) of the virus, with a strong binding energy around 9.7 kcal/mol [58] and interacts with the amino acid residues via alkyl and π- alkyl bonding in the active site at Ala107, Tyr264, Pro248 and through conventional hydrogen bonding with Asp108 [59].

Vanillin, also called vanillic aldehyde, vanillaldehyde, methyl-protocatechualdehyde or 4-hydroxy-3-methoxy benzaldehyde, is the primary constituent of vanilla beans, widely used in many processed foods including chocolates, ice creams, coffee, raspberry, baked goods and beverages, oatmeal, etc. It has been extensively utilized as an antioxidant, flavouring agent and preservatives in a variety of foods, medicines, and perfumes etc., and also reported to have a range of medicinal benefits, such as antitumour, antioxidant, antiviral, anticancer, antibacterial, antifungal, neuroprotective activity etc. *Law and his co-workers* studied twenty vanillin derived Schiff-bases, accompanied by monolaurin as well as tetrodotoxin, and investigated their possible activity as inhibitors of coronavirus-2. Based on ligand-based approach, these twenty compounds exhibited very high M^{pro} inhibition potential attributable to their superior alignment and common features to PDB-5RE6 [60]. In another work reported by *Kun Harismah et al.*, structural analysesof vanillin, along with eleven vanillin derivatives were done via density functional theory calculations. For the formation of ligand-target complexes, RNA-dependent RNA polymerase (RdRp) and the main protease of SARS-CoV-2 were selected as the enzymatic target, while performing MD simulations and it was observed that, among the complexes, derivatives that contain $–NHNH_2$ and $–CH_2Cl$ instead of the aldehydic hydrogen of vanillin, demonstrated best results in inhibiting both RdRp and M^{pro} respectively. Thus, these experiments also indicated the possibility of vanillin derived compounds in the innovation of possible drug against COVID-19 [61].

Ellagic acid or 2,3,7,8-tetrahydroxy-[1]-benzopyranol-[5,4,3-cde]-benzopyran-5,10-dione is a naturally occurring heterotetracyclic polyphenolic compound that can be obtained from gallic acid dimerisation. Ellagic acid is usually produced in plants from tannin hydrolysis like hydrolysis of ellagitannin and geraniin and it is naturally found in different oak species like *Quercus alba* or *Quercus robur*, as well as in *Myriophyllum spicatum* and the medicinal mushroom *Phellinus linetus*. In addition, it has existence in plentiful of vegetables, fruits and other food items [62,63] like raspberries, cranberries, strawberries, pomegranate, cloudberries, boysenberries, grapes, rose hip, plums, walnuts, mango, guava, pecans, almonds, red wine etc., [64- 66]. Ellagic acid revealed its potential to be a drug for COVID-19 treatment owing to its extraordinary binding at the active site of main protease along with significant interaction with the amino acid residue Cys145 [67]. Fourteen phenolic compounds and terpenes, including ellagic acid were tested by *Shaldam and his co-workers*, in order to analyse their binding affinities towards M^{pro} and RdRp enzymes of the SARS-CoV-2 with the help of molecular docking experiments. According to their study, among the tested compounds, ellagic acid and quercetin demonstrated highest activity for SARS-CoV-2 inhibition [68]. Again, *S. Arokiyaraj et al.*, studied the prospective ability of Geranii Herba (*Geranium koreanum*) as a potential inhibitor of SARS-CoV-2. Geranii Herba is a medicinal plant particularly found in Asia which is traditionally used for the treatment of gastrointestinal inflammation disorders and viral infections in some Asian countries. They tested the polyphenolic constituents of Geranii Herba, against SARS-CoV-2 with an in silico approach. The molecular docking analysis indicated the possibility of the constituents of the plant as probable drug candidates for the treatment of COVID-19 infections and reported that phenolic components of the plant, namely ellagic acid, quercetin, geraniin, gallic acid, kaempferol and kaempferitrin have noteworthy binding interactions for the 3-chymotrypsin-like protease ($3CL^{pro}$), receptor binding domain (RBD) of the viral spike (S) protein, and the cell surface receptor glucose-regulated protein-78 of the virus [69]. In addition, the interactions of the components of *Moringa oleifera*, that is basically used as vegetable and traditional herbal medicine for the treatment of viral infections, were studied to analyse their capacity as inhibitor of the main protease of coronavirus-2 via molecular dynamics simulation methodsand ellagic acid, among the constituents of the medicinal plant, demonstrated the highest binding interaction, around 7.1kcal mol^{-1} for nsp9 and around 6.9 kcal mol^{-1} for nsp10, which are vital co-factors for activation of multiple enzyme replication of the virus [70].

Caffeic acid or 3,4-dihydroxycinnamic acid is a hydroxycinnamic acid derivative and is one of the majorcomponents of woody plant biomass. It is available in all plants as an intermediate of lignin biosynthesis in plants. It canbe extracted from many plants like - *Eucalyptus gobulus*, *Hordeum vulgare*, *Dipsacus asperoides*, freshwater fern *Salviniamolesta* and the mushroom *Phellinus linteus* etc. In addition, it is copiously present in foods like coffee, thyme, blueberries, black chokeberries, sage, kiwis, spearmint, cherries, ceylon cinnamon, star anise, apples, sunflower seeds, apricots, oils, prunes, tea and yerba mate herb [71-73]. It has shown various immune-protecting abilities like - antioxidant, antifungal, anti-inflammatory, anticancer, antibacterial and antiviral properties [74-81]. A range of caffeic acid derivativeswere investigated as anti-COVID-19 agent and some significant drug targets of COVID-19, viz., spike glycoprotein ectodomain (open and closed both), Nsp15 endoribonuclease, S2 subunit of spike glycoprotein (6LXT), as well as M^{pro} (6LU7) have been introduced in the experiments. Several derivatives of caffeic acid were identified to be modulators of COVID-19 drug targets, specifically, khainaoside B for fusion protein of the virus, 6-O-Caffeoylarbutin for Nsp15,

khainaoside C as M^{pro} modulator, khainaoside C to be spike protein (open) modulator, and vitexfolin A to be spike protein (closed) modulator [82]. Again, ethanolic extracts of stems of *Sambucus formosana*, commonly known as elderberry, were studied against human coronavirus variant, viz., HCoVNL63 and the extracts exhibited moderately strong efficiency. Successive investigations of the existing phenolic constituents recognized the maximum potential of caffeic acid among all the constituents [83]. It can additionally hinder the penetration of the virus into the receptor cell [83]. In another study,reported by *Mohammad A. I. Al-Hatamleh et al.,* it was reported that caffeic acid, caffeic acid phenethyl ester, chrysin aswell as galangin, demonstrated high ability as the inhibitor of the 3-chymotrypsin-like protease enzyme of the COVID- 19 virus and thereby they can avert enzyme replication [85]. During viral infections, the host receptor spike heat shock protein A5 is found to be upregulated and hence targeted by the spike protein of the virus. Molecular dynamics simulationsanalysis, carried out for monitoring the interacting ability of some phytoestrogens against the Heat Shock Protein FamilyA (Hsp70) Member 5 or HSPA5 substrate-binding domain β, which indicated modest to high binding interaction for a number of tested compounds, including caffeic acid, caffeic acid phenethyl ester, and thymoquinone, designating their potential as coronavirus-2 inhibitors [86,87]. Furthermore, molecular docking investigations disclosed that caffeic acid phenethyl ester exhibited the maximum affinity towards $3CL^{pro}$ and S1 subunit of spike protein [88]. Additionally, caffeicacid interacts to the active site residues Lys50 of main protease via hydrogen bonding as well as with cornavirus-2 structural proteins E and N [86, 89].

Thymol, also known as 2-isopropyl-5-methylphenol is a naturally occurring phenolic monoterpenoid derivate of p-cymene that is largely available in oils of thyme species, *Thymus vulgaris*, and can also be found in a variety of plants including origanum, ajwain, acimum, star anise, crimson, beebalm, eyewort, etc. Thymol has been recognised to be a therapeutic agent indicating diverse range of utilizations, like - as a preservative, expectorant, antiseptic, anaesthetic, antiviral, anti-diarrhoea agent and also for treatment of coughs, headaches and upper respiratory system disorders. *P.K. Yadav et al.,* executed a study using eighteen anti-viral phytoconstituents via in silico molecular docking experiments to analyse their capacity as COVID-19 inhibitors. The structure of TMPRSS 2 or transmembrane protease serine-2, was assumed that assist viral internalization by the cleavage of the spike protein of the virus. Accordingly, docking studies were executed with the catalytic domain of transmembrane protease serine 2 against these eighteen phytochemicals, that resulted thymol to be a superior preventer owing to its strong interaction with transmembrane protease serine 2, causing slight alteration in the structural arrangement in case of catalytic residues [90]. It was also found from in silico analyses that thymol has the potential for proper physical interaction with the coronavirus-2 spike glycoproteins, angiotensin-converting enzyme 2 to block interaction of coronavirus-2 with receptor ACE2, spike glycoprotein of coronavirus-2 beta (B.1.351) variant, transmembrane protease serine 2 and neutrapilin-1 receptors [91].

Rosmarinic acid or 3,4-dihydroxyphenyllactic acid is basically a caffeic acid ester available in a number of plants of the *Lamiaceae* family, such as rosemary, lemon balm, sage, Spanish sage, perilla, marjoram, mint, oregano, basil etc. andit is acknowledged to have an assortment of bioactive properties like - neuroprotective, antioxidant, anti-inflammatory, antidepressant, antiviral, antiapoptotic, antibacterial, hepatoprotective, and anti-nociceptive activity. *Tegen et al.,* [55] predicted that plants demonstrating therapeutic benefits, that contain phytoconstituents like rosmarinic acid or ursolicacid, etc., may have potential against coronavirus-2. Again, *A.G. Junior and his co-workers* reported that, rosmarinic acidis successful in augmenting the levels of Angiotensin-converting enzyme 2, which is an indispensable receptor for cell entry of the SARS-CoV-2 virus, and thereby it might prevent the virus by dropping the host receptors aiding viral endocytosis [92]. Furthermore, according to the work reported by *J. Selvaraj et al.,* rosmarinic acid and ursolic acid can bind themselves efficiently to Nsp15 protein of the virus signifying their prospective function in restraining the viral replication. The RNA-dependent RNA polymerase (RdRp or nsp12) of the SARS CoV-2, the most essential factor for replication and transcription machinery of the coronavirus-2, was also introduced to molecular docking studies with *Plectranthus amboinicus* constituents and the studies also established the possible binding of rosmarinic acid with RdRp of SARS CoV-2 [93].

CONCLUSION

To conclude, the COVID-19 viral infection including different variants of the virus, along with the possibility of occurrence of more new variants that might be more aggressive, transmissible, vaccine-resistant, is becoming one of the major globalconcern for human beings now-a-days. To deal with such an unpredictable widespread outbreak, is a long-standing process that necessitates not only the efforts of each and every individual, but also the worldwide collaborations by healthexperts, research scientists, governments, authorities and the public. Although, the world is in urgent need of novel antiviral therapeutic alternatives to tackle the virus, yet we all know the fact that development and recognition of new medicines are very much time-consuming, considering the mandatory period required for its clinical trials and proper validation. A number of molecular docking experiments have indicated the wide scope of the phytochemicals to be a promising option as therapeutic agents in order to combat COVID-19 as they are proven to be successful in targeting viral protein and blocking viral replication. Nevertheless, in depth in vitro and in vivo experiments are needed for proper understanding of their non-toxicity and restorative concentrations before clinical trials on human. In addition, although these phytochemical constituents are beneficial, their use beyond a specific concentration might be toxic as well. However, the author expects that the phytochemicals reviewed here will assist to add new dimensions towards pre-emptive and restorative strategies against SARS-CoV-2 and its different variants, not only towards the advancement of effectual and secure drugs to tackle COVID-19, but also towards the possible prevention of the disease expansion, by making those constituents a part of regular human diet in order to strengthen the human immunity.

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REFERENCES

1. Deng SQ, Peng HJ. 2020. Characteristics of and public health responses to the coronavirus disease 2019 outbreak in China. J. Clin. Med. 9(2), 575: 1-10
2. Han Q, Lin Q, Jin S and You L. 2020. Coronavirus 2019-nCoV: a brief perspective from the front line. J. Infect. 80: 373–377.
3. Adil MT, Rahman R, Whitelaw D, Jain V, Al-Taan O, Rashid F, Munasinghe A, Jambulingam P. 2021. SARS-CoV-2 and the pandemic of COVID-19. Postgrad Med J. 97: 110–116.
4. Wu T, Leung K, Leung GM. 2020. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. Lancet. 395: 689–697.
5. Hui DS, Azhar E, Madani TA, et al. 2020. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - the latest 2019 novel coronavirus outbreak in Wuhan. China. Intl. J. Infect. Dis. 91: 264–266.
6. Lu R, Zhao X, Li J, et al. 2020. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 395(10224): 565–574.
7. Hu B, Guo H, Zhou P et al. 2021. Characteristics of SARS-CoV-2 and COVID-19. Nat. Rev. Microbiol. 19: 141–154.
8. Cui J, Li F, Shi ZL. 2019. Origin and evolution of pathogenic coronaviruses. Nat. Rev. Microbiol. 17: 181–192.
9. Asrani P, Eapen MS, Hassan MI, Sohal SS. 2021. Implications of the second wave of COVID-19 in India. Lancet Respir. Med. 9: e93–e94.
10. Abd El-Aziz TM, Stockand JD. 2020. Recent progress and challenges in drug development against COVID-19 coronavirus (SARS-CoV-2) - an update on the status. Infect. Genet. Evol. 83, 104327: 1-10
11. Shamsi A, Mohammad T, Anwar S, et al. 2020. Glecaprevir and Maraviroc are high-affinity inhibitors of SARS-CoV-2 main protease: possible implication in COVID-19 therapy. Biosci. Rep. 40 (6): 1-8
12. Chen J, Chen J, Wang R, Hozumi Y, Liu G, Qiu Y, Wei X, Wei Wei G. 2023. Emerging Dominant SARS-CoV-2 Variants. J. Chem. Inf. Model. 63. 1: 335–342.
13. Wolf JM, Wolf LM, Bello GL, Maccari JG, Nasi LA. 2023. Molecular evolution of SARS-CoV-2 from December 2019 to August 2022. J Med Virol. 95(1):e28366.
14. Kotula JJ, Balakumar N, Khan D, Patel B. 2021. COVID-19 and therapeutic drugs repurposing in hand: the need for collaborative efforts. Le Pharm. Hosp. Clin. 56 (1): 3–11.
15. Das A, Pandita D, Jain GK, Agarwal P, Grewal AS, Khar RK, Lather V. 2021.Role of phytoconstituents in the management of COVID-19. Chem. Biol. Interact. 341: 109449.
16. Kumari P, Singh A, Ngasainao MR, Shakeel I, Kumar S, Lal S, Singhal A, Sohal S, Singh IK, Hassan M. 2020. Potential diagnostics and therapeutic approaches in COVID-19. Clin. Chim. Acta. 510: 488–497.
17. Mohammad T, Shamsi A, Anwar S, Umair M, Hussain A, Rehman MT, AlAjmi MF, Islam A, Hassan MI. 2020. Identification of high-affinity inhibitors of SARS-CoV-2 main protease: towards the development of effective COVID-19 therapy. Virus Res. 288:198102.
18. Jairajpuri DS, Hussain A, Nasreen K, Mohammad T, Anjum F, Rehman MT, Hasan GM, Alajmi MF, Hassan MI. 2021. Identification of natural compounds as potent inhibitors of SARS-CoV-2 main protease using combined docking and molecular dynamics simulations. Saudi J. Biol. Sci. 28 (4): 2423–2431.
19. Dos Santos CN, Menezes R, Stewart D. 2018. Polyphenols as new leads in drug discovery: biological activity and mechanisms. Curr. Pharm. Des. 24 (19): 2041–2042.
20. Ali S, Alam M, Hasan GM, Hassan MI. 2021. Potential therapeutic targets of Klebsiella pneumoniae: a multi-omics review perspective. Brief. Funct. Genomics. 21(2): 63-77.
21. Alam M, Ali S, Ashraf GM, Bilgrami AL, Yadav DK, Hassan MI. 2022. Epigallocatechin 3-gallate: from green tea to cancer therapeutics. Food Chem. 379: 132135.
22. Ali S, Alam M, Khatoon F, Fatima U, Elasbali AM, Adnan M, Islam A, Hassan MI, Snoussi M, De Feo V. 2022. Natural products can be used in therapeutic management of COVID-19: Probable mechanistic insights. Biomed Pharmacother. 2022, 147, 112658: 1-11,
23. I. Vujic, L.B. Moore, H.H. LeVeen, Recanalization of occluded superior vena cava for replacement of LeVeen shunt catheter, Radiology 164 (1) (1987) 270–272.
24. Kempuraj D, Castellani ML, Petrarca C, Frydas S, Conti P, Theoharides TC, Vecchiet J. 2006. Inhibitory effect of quercetin on tryptase and interleukin-6 release, and histidine decarboxylase mRNA transcription by human mast cell-1 cell line. Clin. Exp. Med. 6 (4): 150–156.
25. Mink PJ, Scrafford CG, Barraj LM, Harnack L, Hong CP, Nettleton JA, Jacobs Jr DR. 2007. Flavonoid intake and cardiovascular disease mortality: a prospective study in postmenopausal women. Am. J. Clin. Nutr. 85 (3): 895–909.
26. Nair MP, Mahajan S, Reynolds JL, Aalinkeel R, Nair RH, Schwartz SA, Kandaswami C. 2006. The flavonoid quercetin inhibits proinflammatory cytokine (tumor necrosis factor alpha) gene expression in normal peripheral blood mononuclear cells via modulation of the NF-kappa beta system, Clin. Vaccin. Immunol. 13 (3): 319–328.
27. Nieman DC, Henson DA, Gross SJ, Jenkins DP, Davis JM, Murphy EA, Carmichael MD, Dumke CL, Utter AC, McAnulty SR, McAnulty LS, Mayer EP. 2007. Quercetin reduces illness but not immune perturbations after intensive exercise. Med. Sci. Sports Exerc. 39 (9): 1561–1569.
28. Lalani S, Poh CL. Flavonoids as antiviral agents for enterovirus A71 (EV-A71). Viruses. 12(2), 184: 1-34
29. Jasso-Miranda C, Herrera-Camacho I, Flores-Mendoza LK, Dominguez F, Vallejo-Ruiz V, Sanchez-Burgos GG, Pando-Robles V, Santos-Lopez G, Reyes-Leyva J. 2019. Antiviral and immunomodulatory effects of polyphenols on macrophages infected with dengue virus serotypes 2 and 3 enhanced or not with antibodies. Infect. Drug Resist. 12: 1833–1852
30. Vázquez-Calvo Á, Jiménez de Oya N, Martín-Acebes MA, Garcia-Moruno E, J. Saiz JC. 2017. Antiviral properties of the natural polyphenols delphinidin and epigallocatechin gallate against the Flaviviruses West Nile Virus, Zika Virus, and Dengue Virus. Front. Microbiol. 8, 1314: 1-8
31. Mirzaie A, Halaji M, Dehkordi FS, Ranjbar R, Noorbazargan H. 2020. A narrative literature review on traditional medicine options for treatment of corona virus disease 2019 (COVID-19). Complement. Ther. Clin. Pract. 40: 101214.
32. Ganjhu RK, Mudgal PP, Maity H, Dowarha D, Devadiga S, Nag S, Arunkumar G. 2015. Herbal plants and plant preparations as remedial approach for viral diseases. Virusdisease. 26 (4): 225–236.
33. Pillaiyar T, Meenakshisundaram S, Manickam M. 2020. Recent discovery and development of inhibitors targeting coronaviruses. Drug Discov. Today. 25 (4): 668–688.
34. Nieman DC, Henson DA, Gross SJ, Jenkins DP, Davis JM, Murphy EA, Carmichael MD, Dumke CL, Utter AC, McAnulty SR, McAnulty LS, Mayer EP. 2007. Quercetin reduces illness but not immune perturbations after intensive exercise. Med. Sci. Sports Exerc. 39 (9): 1561–1569.
35. Henson D, Nieman D, Davis JM, Dumke C, Gross S, Murphy A, Carmichael M, Jenkins DP, Quindry J, McAnulty S, McAnulty L, Utter A, Mayer E. 2008. Post-160-km race illness rates and decreases in granulocyte respiratory burst and salivary IgA output are not countered by quercetin ingestion. Int. J. Sports Med. 29 (10): 856–863.
36. Alam M, Hasan GM, Hassan MI. 2021. A review on the role of TANK-binding kinase 1 signaling in cancer. Int. J. Biol. Macromol. 183: 2364–2375.

37. Heinz SA, Henson DA, Austin MD, Jin F, Nieman DC. 2010. Quercetin supplementation and upper respiratory tract infection: a randomized community clinical trial. Pharmacol. Res. 62 (3): 237–242.
38. Dahiya R, Mohammad T, Roy S, Anwar S, Gupta P, Haque A, Khan P, Kazim SN, Islam A, Ahmad F, Hassan MI. 2019. Investigation of inhibitory potential of quercetin to the pyruvate dehydrogenase kinase 3: towards implications in anticancer therapy. Int. J. Biol. Macromol. 136: 1076–1085.
39. Yousuf M, Khan P, Shamsi A, Shahbaaz M, Hasan GM, Haque Q, Christoffels Islam AA, Hassan MI. 2020. Inhibiting CDK6 activity by quercetin is an attractive strategy for cancer therapy, ACS Omega. 5 (42): 27480–27491
40. Yi L, Li Z, Yuan K, et al. 2004. Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. J. Virol. 78 (20): 11334–11339.
41. Colunga Biancatelli RML, Berrill M, Catravas JD, Marik PE. 2020. Quercetin and vitamin C: an experimental, synergistic therapy for the prevention and treatment of SARS-CoV-2 related disease (COVID-19). Front. Immunol. 11: 1451.
42. Kulyar MF, Li R, Mehmood K, Waqas M, Li K, Li J. 2020. Potential influence of *Nagella sativa* (Black cumin) in reinforcing immune system: a hope to decelerate the COVID-19 pandemic, Phytomedicine. 85: 153277.
43. Xu H, Liu B, Xiao Z, Zhou M, Ge L, Jia F, Liu Y, Jin H, Zhu X, Gao J, Akhtar J, Xiang B, Tan K, Wang G. 2021. Computational and experimental studies reveal that thymoquinone blocks the entry of coronaviruses into in vitro cells. Infect. Dis. Ther. 10 (1): 483–494.
44. Islam MN, Hossain KS, Sarker PP, Ferdous J, Hannan MA, Rahman MM, Chu DT, Uddin MJ. 2020. Revisiting pharmacological potentials of *Nigella sativa* seed: a promising option for COVID-19 prevention and cure. Phytother. Res. 35 (3): 1329–1344.
45. Rahman MT. 2020. Potential benefits of combination of *Nigella sativa* and Zn supplements to treat COVID-19. J. Herb. Med. 23: 100382.
46. Pironi AM, de Araújo PR, Fernandes MA, Salgado H, Chorilli M. 2017. Characteristics, biological properties and analytical methods of ursolic acid: a review. Crit. Rev. Anal. Chem. 48 (1): 86–93.
47. Shanmugam MK, Dai X, Kumar AP, Tan BKH, Sethi G, Bishayee A. 2013. Ursolic acid in cancer prevention and treatment: molecular targets, pharmacokinetics and clinical studies, Biochem. Pharmacol. 85 (11): 1579–1587.
48. L´opez-Hortas L, P´erez-Larr´an P, Gonz´alez-Mu˜noz MJ, Falqu´e E, Domínguez H. 2018. Recent developments on the extraction and application of ursolic acid. A review. Food Res. Int. 103: 130–149.
49. Mlala S, Oyedeji AO, Gondwe M, Oyedeji OO. 2019. Ursolic acid and its derivatives as bioactive agents, Molecules. 24, 15: 2751
50. Son J, Lee SY. 2020. Therapeutic potential of ursonic acid: comparison with ursolic acid. Biomolecules. 10: 11
51. Singh DD, Verma R, Tripathi SK, Sahu R, Trivedi P, Yadav DK. 2021. Breast cancer transcriptional regulatory network reprogramming by using the CRISPR/Cas9 system: an oncogenetics perspective. Curr. Top. Med. Chem. 21: 2800–2813.
52. Dwivedi GR, Rai R, Pratap R, Singh K, Pati S, Sahu SN, Kant R, Darokar MP, Yadav DK. 2021. Drug resistance reversal potential of multifunctional thieno[3,2-c]pyran via potentiation of antibiotics in MDR P. aeruginosa. Biomed. Pharmacother. 142: 112084.
53. Alam M, Ali S, Mohammad T, Hasan GM, Yadav DK, Hassan MI. 2021. B Cell lymphoma 2: a potential therapeutic target for cancer therapy. Int. J. Mol. Sci. 22 (19): 10442.
54. Alam M, Ali S, Ahmed S, Elasbali AM, Adnan M, Islam A, Hassan MI, Yadav DK. 2021.Therapeutic potential of ursolic acid in cancer and diabetic neuropathy diseases, Int. J. Mol. Sci. 22 (22): 12162.
55. Tegen D, Dessie K, Damtie D. 2021. Candidate anti-COVID-19 medicinal plants from ethiopia: a review of plants traditionally used to treat viral diseases. Evid. Based Complement. Altern. Med. 2021, 6622410:1-20
56. Mishra P, Sohrab S, Mishra SK. 2021. A review on the phytochemical and pharmacological properties of *Hyptis suaveolens* (L.). Poit, Future J. Pharm. Sci. 7 (1): 65
57. Kumar A, Choudhir G, Shukla SK, Sharma M, Tyagi P, Bhushan A, Rathore M. 2020. Identification of phytochemical inhibitors against main protease of COVID-19 using molecular modeling approaches. J. Biomol. Struct. Dyn. 39 (10): 3760–3770.
58. Halder P, Pal U, Paladhi P, Dutta S, et al. 2022 Evaluation of potency of the selected bioactive molecules from Indian medicinal plants with M(Pro) of SARS-CoV-2 through in silico analysis. J. Ayurveda Integr. Med. 13(2):100449.
59. Mitra D, Verma D, Mahakur B, et. al. 2021. Molecular docking and simulation studies of natural compounds of *Vitex negundo* L. against papain-like protease (PL(pro)) of SARS CoV-2 (coronavirus) to conquer the pandemic situation in the world. J. Biomol. Struct. Dyn. 40(12):5665-5686
60. Law WY, Asaruddin MR, Bhawani SA, Mohamad S. 2020. Pharmacophore modelling of vanillin derivatives, favipiravir, chloroquine, hydroxychloroquine, monolaurin and tetrodotoxin as M(Pro) inhibitors of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). BMC Res. Notes. 13 (1): 527.
61. Harismah K, Fazeli F, Zandi H. 2022. Structural analyses of vanillin derivative compounds and their molecular mocking with MPro and RdRp enzymes of COVID-19. 12(2): 1660-1669
62. Evtyugin DD, Magina S, Evtuguin DV. 2020. Recent advances in the production and applications of ellagic acid and its derivatives. A review. Molecules. 25(12): 2745
63. Malini P, Kanchana G, Rajadurai M. 2011. Antibiabetic efficacy of ellagic acid instreptozotocin-induced diabetes mellitus in albino wistar rats. Asian J. Pharm. Clin. Res. 4 (3): 124–128.
64. Rangkadilok N, Worasuttayangkurn L, Bennett RN, Satayavivad J. 2005. Identification and quantification of polyphenolic compounds in Longan (*Euphoria longana* Lam.) fruit, J. Agric. Food Chem. 53 (5): 1387–1392.
65. Plundrich N, Grace MH, Raskin I, Ann Lila M. 2013. Bioactive polyphenols from muscadine grape and blackcurrant stably concentrated onto protein-rich matrices for topical applications. Int. J. Cosmet. Sci. 35 (4): 394–401.
66. Türk G, Sönmez M, Ceribaşi AO, Yüce A, Ateşşahin A. 2010. Attenuation of cyclosporine A-induced testicular and spermatozoal damages associated with oxidative stress by ellagic acid, Int. Immunopharmacol. 10 (2): 177–182.
67. Pandey AK, Verma S. 2020. An in-silico evaluation of dietary components for structural inhibition of SARS-Cov-2 main protease. J. Biomol. Struct. Dyn. 40(1):136-142
68. Shaldam MA, Yahya G, Mohamed NH, Abdel-Daim MM, Al Naggar Y. 2021. In silico screening of potent bioactive compounds from honeybee products against COVID-19 target enzymes, Environ. Sci. Pollut. Res. Int., 28(30): 40507–40514.
69. Arokiyaraj S, Stalin A, Kannan BS, Shin H. 2020. Geranii herba as a potential inhibitor of SARS-CoV-2 main 3CL(pro), spike RBD, and regulation of unfolded protein response: an in silico approach. Antibiotics. 9 (12): 836
70. Muhammad S, Hassan SH, Al-Sehemi AG, Shakir HA, Khan M, Irfan M, Iqbal J. 2021. Exploring the new potential antiviral constituents of *Moringa oliefera* for SARS-COV-2 pathogenesis: an in silico molecular docking and dynamic studies. Chem. Phys. Lett. 767: 138379.
71. El-Seedi HR, El-Said AM, Khalifa SA, G¨oransson U, Bohlin L, Borg- Karlson AK, Verpoorte R. 2012. Biosynthesis, natural sources, dietary intake, pharmacokinetic properties, and biological activities of hydroxycinnamic acids. J. Agric. Food Chem. 60 (44): 10877–10895.
72. Del Rio D, Rodriguez-Mateos A, Spencer JP, Tognolini M, Borges G, Crozier A. 2012. Dietary (poly)phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. Antioxid. Redox Signal. 18 (14): 1818–1892.
73. M. Sova M, Saso L. 2020. Natural sources, pharmacokinetics, biological activities and health benefits of hydroxycinnamic acids and their metabolites. Nutrients. 12(8): 2190.
74. Sud'ina GF, Mirzoeva OK, Pushkareva MA, Korshunova GA, Sumbatyan NV, Varfolomeev SD. 1993. Caffeic acid phenethyl ester as a lipoxygenase inhibitor with anti-oxidant properties. FEBS Lett. 329 (1–2): 21–24.
75. Russo A, Longo R, Vanella A. 2002. Anti-oxidant activity of propolis: role of caffeic acid phenethyl ester and galangin. Fitoterapia. 73 Suppl. 1: S21–S29.
76. Jung WK, Choi I, Lee DY, Yea SS, Choi YH, Kim MM, Park SG, Seo SK, Lee SW, Lee CM, Park YM, Choi IW. 2008. Caffeic acid phenethyl ester protects mice from lethal endotoxin shock and inhibits lipopolysaccharide-induced cyclooxygenase-2 and inducible nitric oxide synthase expression in RAW 264.7 macrophages via the p38/ERK and NF-kappaB pathways. Int. J. Biochem. Cell Biol. 40 (11): 2572–2582.

77. Doiron JA, Leblanc LM, H´ebert MJ, Levesque NA, Par´e AF, Jean- François J, Cormier M, Surette ME, Touaibia M. 2016. Structure-activity relationship of caffeic acid phenethyl ester analogs as new 5-lipoxygenase inhibitors. Chem. Biol. Drug Des. 89 (4): 514–528.
78. Natarajan K, Singh S, Burke Jr TR, Grunberger D, Aggarwal BB. 1996. Caffeic acid phenethyl ester is a potent and specific inhibitor of activation of nuclear transcription factor NF-kappa B. Proc. Natl. Acad. Sci. USA 93 (17): 9090–9095.
79. Ali S, Ehtram A, Arora N, Manjunath P, Roy D, Ehtesham NZ, Hasnain SE. 2021. The M. tuberculosis Rv1523 methyltransferase promotes drug resistance through methylation-mediated cell wall remodeling and modulates macrophages immune responses. Front. Cell Infect. Microbiol. 11: 622487.
80. Arasoglu T, Derman S, Mansuroglu B. 2015. Comparative evaluation of antibacterial activity of caffeic acid phenethyl ester and PLGA nanoparticle formulation by different methods. Nanotechnology 27 (2): 025103.
81. Erdemli HK, Akyol S, Armutcu F, Akyol O. 2015. Antiviral properties of caffeic acid phenethyl ester and its potential application. J. Intercult. Ethnopharmacol. 4 (4): 344–347.
82. Adem S, Eyupoglu V, Sarfraz I, Rasul A, Zahoor AF, Ali M, Abdalla M, Ibrahim IM, Elfiky AA. 2020. Caffeic acid derivatives (CAFDs) as inhibitors of SARS-CoV-2: CAFDs-based functional foods as a potential alternative approach to combat COVID-19. Phytomedicine. 85: 153310.
83. Weng JR, Lin CS, Lai HC, Lin YP, Wang CP, Tsai YC, Wu KC, Huang SH, Lin CW. 2019. Antiviral activity of *Sambucus FormosanaNakai* ethanol extract and related phenolic acid constituents against human coronavirus NL63. Virus Res. 273: 197767.
84. Wang GF, Shi LP, Ren YD, et. al. 2009. Anti-hepatitis B virus activity of chlorogenic acid, quinic acid and caffeic acid in vivo and in vitro, Antivir. Res. 83 (2): 186–190.
85. Al-Hatamleh MAI, Hatmal MM, Sattar K, Ahmad S, Mustafa MZ, Bittencourt MDC, Mohamud R. 2020. Antiviral and immunomodulatory effects of phytochemicals from honey against COVID-19: potential mechanisms of action and future directions. Molecules. 25(21): 1-23
86. Bhowmik D, Nandi R, Jagadeesan R, Kumar N, Prakash A, Kumar D. 2020. Identification of potential inhibitors against SARS-CoV-2 by targeting proteins responsible for envelope formation and virion assembly using docking based virtual screening, and pharmacokinetics approaches. Infect. Genet. Evol. 84: 104451.
87. Elfiky AA. 2020. Natural products may interfere with SARS-CoV-2 attachment to the host cell. J. Biomol. Struct. Dyn. 39 (9): 3194–3203
88. Refaat H, Mady FM, Sarhan HA, Rateb HS, Alaaeldin E. 2020. Optimization and evaluation of propolis liposomes as a promising therapeutic approach for COVID-19. Int. J. Pharm. 592: 120028.
89. Kumar V, Dhanjal JK, Kaul SC, Wadhwa R, Sundar D. 2020. Withanone and caffeic acid phenethyl ester are predicted to interact with main protease (M(pro)) of SARS-CoV-2 and inhibit its activity. J. Biomol. Struct. Dyn. 39 (11): 3842–3854
90. Yadav PK, Jaiswal A, Singh RK. 2021. In silico study on spice-derived antiviral phytochemicals against SARS-CoV-2 TMPRSS2 target. J. Biomol. Struct. Dyn. 40(22):11874-11884.
91. Rolta R, Salaria D, Sharma P, Sharma B, Kumar V, Rathi B, Verma M, Sourirajan A, Baumler DJ, Dev K. 2021. Phytocompounds of *Rheum emodi*, *Thymus serpyllum,* and *Artemisia annua* inhibit spike protein of SARS-CoV-2 binding to ACE2 receptor: in silico approach. Curr. Pharmacol. Rep. 7(4): 135-149
92. Junior AG, Tolouei S, Dos Reis Lívero FA, Gasparotto F, Boeing T, de Souza P. 2021. Natural agents modulating ACE-2: a review of compounds with potential against SARS-CoV-2 infections, Curr. Pharm. Des. 27 (13): 1588–1596.
93. Selvaraj J, Rekha UV, Jh SF, Sivabalan V, Ponnulakshmi R, Vishnupriya V, Kullappan M, Sreekandan RN, Mohan SK. 2021. Molecular docking analysis of SARS-CoV-2 linked RNA dependent RNA polymerase (RdRp) with compounds from *Plectranthus amboinicus*, Bioinformation. 17 (1): 167–170