

Review Article : Open Access

Special Issue1 (COVID-19)

Ameliorative potential of phytochemicals against side effects of COVID-19 drugs: A review

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Article Info

Article history

Received 1 April 2021

Revised 17 May 2021

Accepted 18 May 2021

Published Online 30 June 2021

Keywords

Drugs

COVID-19

Side effects

Phytochemicals

Ameliorating effect

Abstract

The pandemic of coronavirus disease-19 (COVID-19) remains to nag human race with its more infectious second wave in most of highly populated countries including India. Till date, no specific antiviral drug is discovered or developed which is cent-per-cent effective against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative agent of COVID-19. The efficacy of developed vaccines are said to reduce severity of disease, but the mutation led to origin of more infectious variants. In such scenario, medical management of COVID-19 largely depends upon repurposed drugs like azithromycin, remdesivir, chloroquine, hydroxychloroquine and tocilizumab. However, none of these repurposed drugs is devoid of side effects or drug-induced toxicities which may be fatal too sometimes. Scientific research literature on phytochemicals hints that these miracle phytomolecules may not only be useful in direct therapeutic effect but also have potential to reduce or ameliorate the side-effects of current repurposed drugs used in treatment of COVID-19. This review critically elaborates the side-effects of COVID-19 drugs and the six potential phytochemicals, viz., quercetin, baicalin, kaempferol, curcumin, catechins and gingerols which have potentials to ameliorate such side-effects. The very purpose of the review paper is to promote the scientific studies on these phytomolecules in the management of COVID-19, as there are predictions that human kind has to learn to live with this disease.

1. Introduction

Coronavirus disease-19 (COVID-19) spread is the pandemic condition, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). World health organization had confirmed cases of the disease in December, 2019 and declared it as pandemic in 2020 (WHO, 2020). Since the outbreak of the COVID-19, more than 1 million people have lost their lives due to the pandemic, and the global economy is expected to contract by a staggering nearly about 4.3 per cent in 2020 (UN, 2020). Till date, no treatment has shown 100 per cent efficacy against this disease due to wide range of symptoms and sequelae. Researchers and clinicians are trying various therapeutic regimens for this disease by applying their experience and the knowledge. Certain herbal medicines containing active phytochemicals reported to possess antimicrobial, antiviral, anti-inflammatory and immunostimulant properties. The immunomodulatory effect of the drug is believed to be beneficial against COVID-19 (Nugraha *et al.*, 2020). However, multiple drug usage to manage COVID-19 and the chances of drug-drug interaction with more complicated side may be possible especially in old age and comorbid patients.

Therapeutic management of COVID-19 includes infection prevention, use of efficacious drugs, supportive care particularly oxygen supply with mechanical ventilator as and when needed. The FDA has approved the drug, remdesivir, for the treatment of COVID-19 positive patients. Favipiravir was first used against SARS-CoV-2 in Wuhan. In June 2020, favipiravir received the DCGI approval in India for mild and moderate COVID-19 infections (Agrawal *et al.*, 2020). Till date, various drugs have been tested and approved to be use in emergency for the treatment of patients having COVID-19, particularly to save the life of the severely affected patients.

Azithromycin exhibited a synergistic antiviral effect towards SARS-CoV-2, whilst mixed with hydroxychloroquine both *in vitro* and in a clinical setting (Andreani *et al.*, 2020; Gautret *et al.*, 2020). Azithromycin up-regulates the production of type I and III interferons (specifically interferon- β and interferon- λ), and genes involve in virus reputation including MDA5 and RIG-I (Schögler *et al.*, 2015; Menzel *et al.*, 2016; Li *et al.*, 2019). Azithromycin regulates and/or decreases the production of IL-1 β , IL-6, IL-8, IL-10, IL-12, and IFN- α (Zarogoulidis *et al.*, 2012; Cai *et al.*, 2013). Hydroxychloroquine also has immunomodulatory effects, and has been reported to decrease various ILs, IFN- α , and tumor necrosis factor (Silva *et al.*, 2013). Azithromycin and Hydroxychloroquine, both decrease the production of major inflammatory cytokines such as IL-1 and IL-6. These mechanisms are universally concerned inside the innate response towards infectious agents, and probably towards SARS-CoV-2. During the therapeutic use of drugs in COVID-19 patient, many side effects and adverse events may be encountered which lead to complications in severely affected patients who may have

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compromised function of vital organs. Thus, the side effects of the drugs, which are used in COVID-19 patients, should be minimized through use of combination of drugs with proper therapeutic drug monitoring and use of various phytochemicals or plant based remedies. There are various reports of efficacy of phytomedicine with ameliorating effect against drug or toxicant-induced side effects. We believe that simultaneous treatment with phytochemicals may have important role to minimize the side effects of COVID-19 drugs. However, such drug-drug interaction studies should be done before use of such combination or consultation of physician is must to avoid possible drug-drug interactions.

Key focus of this review is to highlight the significant information about mechanism of action, side effects and interaction of drugs which are being used for COVID-19 as well as ameliorating potential of few key phytochemicals against side-effects caused by common COVID-19 drugs. This review would further be helpful the scientific community involved in designing efficacious and safe therapeutic regimen for the treatment of COVID-19.

2. COVID-19 drugs and their side effects

2.1 Lopinavir/Ritonavir (Protease inhibitors)

Lopinavir is generally co-formulated with ritonavir as a fixed-dose combination. This combination is primarily used as an antiretroviral drug and demonstrated good clinical efficacy in HIV-infected patients of all the groups (Chandwani and Shuter, 2008). Both lopinavir and ritonavir are protease inhibitors class of antiretroviral drugs and are effective against HIV-1 (Human immunodeficiency virus-1). Protease inhibitors class of drugs bind and inactivate viral proteases to stop viral replication, and thus prevent infected cells to form competent new virions. Viral proteases are specific and unique in structure for each virus. Recently, the crystal structure of the main protease of SARS-CoV-2 is elucidated which closely resembles the protease of SARS-CoV-1 (Zhang *et al.*, 2020a). Lopinavir is three to four times more active against HIV than ritonavir. However, ritonavir, a potent inhibitor of cytochrome P450 3A4, is combined with lopinavir to increase the blood levels of lopinavir which otherwise exhibits poor bioavailability (Corbett *et al.*, 2002; Cvetkovic and Goa, 2003). Thus, ritonavir is combined with lopinavir to increase its plasma half-life through the inhibition of cytochrome P450 enzymes. The use of lopinavir-ritonavir combination in the treatment for severe acute respiratory syndrome (SARS), along with standard treatment protocol, was associated with improved clinical outcomes (Chan *et al.*, 2003). Despite of above research findings, the administration of lopinavir-ritonavir did not result in clinical improvement or lower mortality among COVID-19 patients (Cao *et al.*, 2020). Even though, the lopinavir-ritonavir combination has been advocated as a treatment option against COVID-19, as the pandemic diffusion of SARS-CoV-2 is causing shortages of alternative drugs (Havlichek, 2020).

Regarding the toxicity of lopinavir-ritonavir in COVID-19 patients, gastrointestinal adverse events including anorexia, nausea, vomiting, abdominal discomfort, and diarrhea have been reported to be more common. A serious adverse effect like acute gastritis was also reported. In few COVID-19 patients, self-limiting skin eruptions were also discernible (Cao *et al.*, 2020). Hepatotoxicity, with increased activity of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), was reported with the use of both ritonavir and lopinavir in separate studies (Sulkowski *et al.*, 2000; Nunez, 2006). Previous use of drug combination lopinavir-ritonavir is associated with the

risks of cutaneous eruptions, pancreatitis, QT prolongation, and the potential for multiple drug interactions due to CYP3A inhibition. Adverse effects of lopinavir-ritonavir with very low incidences include allergic reaction, asthenia, myalgias, arthralgias, myocardial infarction, seizures, and lactic acidosis (Chandwani and Shuter, 2008). The use of protease inhibitors like lopinavir-ritonavir was also characterized by the risk of hypercholesterolemia with decreased high-density lipoprotein (HDL) cholesterol levels, increased triglyceride levels and increased low-density lipoprotein (LDL) cholesterol levels resulting in dyslipidemia. These occur due to disruptions of the mechanisms responsible for intracellular synthesis, storage and release of cholesterol (Nolan *et al.*, 2005).

2.2 Favipiravir and Remdesivir (Nucleotide analogues)

Favipiravir was developed by Toyama Chemical Co. Ltd., Japan, in 2013 for the treatment of a broad range of influenza viruses and other RNA viruses (Furuta *et al.*, 2013), whereas remdesivir was primarily developed by Gilead Sciences, United States, in 2017 for the treatment of Ebola virus infection (Siegel *et al.*, 2017). Both antiviral drugs like favipiravir (a guanine analogue) and remdesivir (a C-nucleoside analogue) are prodrugs and metabolized into their active forms in the body. These drugs act on the early to intermediate stage of viral replication by inhibiting the RNA-dependent RNA polymerase. Nucleotide analogues incorporate a mimicking base into the replicating strand from which viral RNA polymerase can not elongate (Chary *et al.*, 2020) and prevents the replication of the viral genome which result in premature termination. Favipiravir was approved as the first anti-COVID-19 drug in China, whereas, emergency use of remdesivir has been approved by the FDA for the treatment of COVID-19 (Nittari *et al.*, 2020). Member drugs of nucleoside analogue class not only suppress viral polymerase but also known to inhibit mitochondrial DNA polymerase-gamma, resulting the decreased mitochondrial DNA and synthesis of mitochondrial proteins. The mitochondrial toxicity is the basis of most of adverse effects of this class of drugs (Moyle, 2000). However, remdesivir has a relatively low affinity for human RNA polymerase II and human mitochondrial RNA polymerase and, therefore expected to have an encouraging safety profile in humans (Pardo *et al.*, 2020). The reversible common adverse effect of remdesivir is increase in hepatic aspartic transaminase (AST) or alanine aminotransferase (ALT). As evident from controlled clinical trials, repeated doses of remdesivir were well-tolerated except with a reversible increase in ALT and AST. *In vitro* studies indicated that increased membrane permeability and intracellular drug metabolism were probable reasons for hepatotoxicity. Interestingly, kidney was also identified as the target organ of side-effects for remdesivir in experimental animals like rats and monkeys (WHO, 2018). A need for continuous monitoring for hepatotoxicity in patients receiving remdesivir has been advocated, keeping in view the interaction between remdesivir and P-glycoprotein inhibitors (Leegwater *et al.*, 2020). In a compassionate use cohort study on remdesivir in a small population of COVID-19 patients, the adverse effects noticed were hepatic enzymes elevation, renal impairment, maculopapular rash, and multiple-organ-dysfunction syndrome, in one or two patients (Grein *et al.*, 2020). In a placebo-controlled randomized trial of remdesivir in the larger population of patients with severe COVID-19 infection, the most common adverse effects noted in the remdesivir treatment group were constipation, hypoalbuminaemia, hypokalaemia, anaemia, thrombocytopenia, and increased total bilirubin (Wang *et al.*, 2020a).

Favipiravir is generally well tolerated but known to cause transient hyperuricaemia in a dose-dependent and reversible manner without posing any clinical manifestation (Pilkington *et al.*, 2020). In a randomized clinical trial of favipiravir with COVID-19 patients, the most common adverse effects were elevated serum uric acid level, liver enzyme abnormalities, and gastrointestinal symptoms (Chen *et al.*, 2020). In phase II/III multicenter randomized clinical trial on patients with moderate COVID-19, adverse drug reactions to favipiravir include diarrhoea, nausea, vomiting, and an increase in hepatic transaminase levels (Ivashchenko *et al.*, 2020). One of the serious side effects of favipiravir is teratogenicity and so, it should not be used in pregnant women (Dongyuan *et al.*, 2020). The major safety concerns that remain associated with the use of favipiravir are hyperuricaemia, teratogenicity and QTc prolongation. Favipiravir appears to be safe and tolerable in short-term use, however, more evidence is needed to assess the long-term effects of treatment (Pilkington *et al.*, 2020).

2.3 Azithromycin (Macrolide antibiotic)

Azithromycin is macrolide antibacterial drug but has been proposed as a potential therapy for the SARS-CoV-2 pneumonia (Parnham *et al.*, 2014). Intracellular accumulation of azithromycin leads to increase in the pH of trans-golgi network which may alter glycosylation of human angiotensin converting enzyme 2 (hACE2) receptor and alters the binding of SARS-CoV-2 virus to respiratory cells (Nujic *et al.*, 2012). Since, the spike protein of SARS-CoV-2 displays a ganglioside binding site and azithromycin mimic the ganglioside, it may inhibit SARS-CoV-2 infection by binding to this site (Gautret *et al.*, 2020). In addition, azithromycin may interfere in the spike protein/CD147 interaction or CD147 expression (Poschet *et al.*, 2020).

Azithromycin is generally well tolerated, but its relatively common adverse effects (1-5% of patients) include gastrointestinal upset, headache and dizziness (Zuckerman *et al.*, 2009). Moreover, hepatotoxicity after azithromycin therapy in patients with increased level of liver enzyme and other clinical symptoms were also reported (Chandrupatla *et al.*, 2002; Das, 2011; Martinez *et al.*, 2015). The mechanism is postulated to be hypersensitivity mediated with subsequent metabolite dependent lesions leading to ductal cholestasis. Its hepatotoxic effect is believed to be intrinsic because liver damage seems to occur in several hours to days (Lalaket *et al.*, 1993). Azithromycin weakly blocks potassium channels across the cardiac membrane which slows cardiac repolarization and QTc prolongation (Giudicessi *et al.*, 2013). Combination of azithromycin with hydroxychloroquine may aggravate the cardiac toxicity (Hache *et al.*, 2021). The public version of eudravigilance, the European Medicines Agency's Adverse Drug Reactions (ADR) database had reported cases of QT prolongation, arrhythmia and cardiac arrest in few patients treated with azithromycin (Sultana *et al.*, 2020). Azithromycin should be used cautiously in patients who are also taking QT-prolonging medications like potassium channel blocker and other antiarrhythmic drugs as well as some antidepressant and antipsychotic drugs.

2.4 Chloroquine and hydroxychloroquine (Aminoquinolines)

Chloroquine and hydroxychloroquine, introduced before 1960, were used to treat malaria and chronic inflammatory diseases like rheumatoid arthritis and systemic lupus erythematosus, and have re-emerged as repurposed drugs to treat viral diseases, including

coronavirus disease 2019 (COVID-19). Several mode of actions were reported to inhibit viral entry, uncoating, assembly and budding, viz., 'a') chloroquine inhibits the viral entry by inhibiting quino-nereductase 2, which is required for the biosynthesis of sialic acid (Kwiek *et al.*, 2004; Tortorici *et al.*, 2019) and by interfering with the glycosylation of its cellular receptor angiotensin converting enzyme 2 receptor (ACE2) (Hofmann *et al.*, 2020), 'b') it inhibits early stage of virus replication by inhibiting virus-endosome fusion, likely via increasing endosomal pH (Khan *et al.*, 2010; Yang *et al.*, 2004), c) it impairs posttranslational modifications of viral proteins through interfering with proteolytic processes and inhibition of glycosylation via specific interactions with sugar modifying enzymes or glycosyltransferases (Randolph *et al.*, 1990), 'd') it hampers the lysosomal protein degradation and lysosomal fusion with auto phagosomes (Savarino *et al.*, 2011; Hashem *et al.*, 2020).

Chloroquine and hydroxychloroquine were reported to have narrow therapeutic ranges (Taylor and White, 2004). The side effects of chloroquine and hydroxychloroquine involve structural and functional changes in heart (myocardial remodeling) like an increase in cardiomyocyte size (causing hypertrophy or dilatation), alterations of the ultramicroscopic structure (*e.g.*, loss of T-tubules) (Louch *et al.*, 2004), modifications of the extracellular matrix, and proliferation of myofibroblasts with development of fibrosis, altered expression of ion channels (*e.g.*, K⁺ channels, L-type Ca²⁺ channels, connexins, ryanodine receptors, *etc.*), transporters (*e.g.*, Na⁺-Ca²⁺ exchangers, sarcoplasmic reticulum ATPases, *etc.*) and other proteins (Mubagwa, 2020). Structural and functional alterations are manifested as conduction disturbances (bundle-branch block, incomplete or complete atrioventricular block, QT prolongation and subsequent torsade de pointes) and cardiomyopathy (hypertrophy and congestive heart failure) (Gevers *et al.*, 2020). Further, gastrointestinal symptoms (nausea and diarrhea) and psychiatric side effects (sleeplessness, agitation, psychosis, depression, anxiety, aggressiveness and confusion) have also been reported.

In addition, chloroquine inhibits autophagy, an important homeostatic mechanism which results in myocardial ischaemia and reperfusion (Sciarretta *et al.*, 2018). Chloroquine has also been shown to be nephrotoxic by autophagy-dependent as well as autophagy independent pathways, including interference with the cyclic adenosine monophosphate production and signaling in distal tubular cells (Wang *et al.*, 2020b). In other preclinical studies, chloroquine inhibits autophagy and worsens ischemic cardiac injury (Ma *et al.*, 2012) and sepsis-induced liver or lung injury (Lin *et al.*, 2014; Zhao *et al.*, 2019). Moreover, chloroquine may lead to endothelial dysfunction due to oxidative stress and decreased nitric oxide production secondary to lysosomal accumulation of fatty acid substrates (Gregório *et al.*, 2021). Recently, it has been reported that the high mortality of severe COVID-19 has been related to micro or macrothrombosis, *i.e.*, to endothelial cell injury by decreasing nitric oxide production and increasing ROS levels (Philipponnet *et al.*, 2020). Over and above the general safety profile of chloroquine and hydroxychloroquine, adverse reactions/side effects may interfere with the clinical outcome of COVID-19 patient. Several scientific documentations associated oxidative stress with changes found in patients with COVID-19, such as its participation in the amplification and perpetuation of the cytokine storm, coagulopathy, and cell hypoxia. In this regard, the therapeutic strategy has been suggested to reduce oxidative stress using antioxidants, NF-κB inhibitors, Nrf2

activators, and iron complexing agents (Cecchini *et al.*, 2020). Thus, concurrent use of phytochemicals like piperine, quercetin/rutin and catechin may reduce the risk of adverse effect/side effect and improve patient compliance during chloroquine and hydroxychloroquine therapy.

2.5 Tocilizumab (Humanized monoclonal antibody)

Tocilizumab, a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R), is an immunosuppressive drug, mainly used for the treatment of rheumatoid arthritis (RA) and systemic juvenile idiopathic arthritis (Rubbert-Roth *et al.*, 2018) and recently introduced for cytokine release syndrome (to prevent cytokine storm) in the coronavirus disease 2019 (COVID-19). Tocilizumab blocks IL-6 receptors and, thereby blocking the assembling of the activated complex of IL-6 and the trans-membrane protein (gp130), which in turn stimulates regulatory B cells, and reduces the expression of inflammatory cytokines (Zhao *et al.*, 2021). IL-6 receptor is expressed on cell surface of macrophages, neutrophils, CD4⁺ T-cells, podocytes, and hepatocytes while the gp 130 is expressed ubiquitously by all the cells (Mauer *et al.*, 2015). Interleukin (IL)-6 is one of the key inflammatory cytokines in the development of SARS induced inflammation, which raises the insufficiency of alveolar blood gas exchange and eventually leads to lung fibrosis and organ failure. IL-6 promotes B and T cells differentiation, acute phase protein production and osteoclast activation; hence tocilizumab treatment thereby has been theorized to play a significant role in inducing immunomodulatory effects in COVID-19 patients (Zhou *et al.*, 2020).

A meta-analysis study with moderate to severe rheumatoid arthritis patient was considered for efficacy and safety evaluation of tocilizumab alone and it was found that serious adverse events like infections along with mild abnormality in the lipid profile, the liver function test, and reaction at injection site were common (Chaudhry and Singh, 2020). COVID patients, who received tocilizumab were more than twice as likely to develop a superinfection as untreated controls, driven primarily by an increase in ventilator-associated pneumonia and *Staphylococcus aureus* accounted for approximately 50% of the bacterial pneumonias in both groups (Somers *et al.*, 2020). In safety study of tocilizumab in COVID-19, it was observed that late-onset infections were more common on long-term follow-up of recipients of tocilizumab and a higher number of cases had tocilizumab-related complications like deranged liver function tests and infusion-related allergic reactions (Pettit *et al.*, 2020).

The class of drug, mechanism of action, side effects of drugs used in the management of COVID-19 also summarized in Table 1.

3. Ameliorating potential of phytochemicals against side effects of COVID-19 drugs

Phytochemicals, the non-nutritive chemical substances derived from vegetation, play a sizeable role in disease prevention. Phytochemicals which includes secondary metabolites and antioxidants have critical medicinal residences. The protective effects of these phytochemicals have been determined in many human illnesses and ailments. A wide variety of natural compounds present in food materials have been reported to have antioxidant properties. Flavonoids are the most common bioactive compounds found in medicinal vegetation (Pietta, 2000). They have shown several preventive action in various ailments due to having antimicrobial, antioxidant, anticancer and anti-inflammatory effects (Cushnie and Lamb, 2005; Procházková *et al.*,

2011; Chirumbolo, 2012). Flavonoids, polyphenols, alkaloids, glycosides, saponins, carbohydrates and vitamins are important phytochemicals, belonging to secondary metabolites of plants. Amongst these secondary metabolites, flavonoids and polyphenols are having important role in prevention of progression of diseases state and reduction of cellular damage caused by xenobiotics such as toxicants and drugs. In this second part of review, information on mechanism of action and ameliorating potential of phytochemicals against COVID-19 drugs' side effects are critically reviewed and discussed.

3.1 Quercetin (Flavonoid)

Quercetin, a flavonoid found in variety of foods including apples, berries, grapes, onion, tomatoes, nuts, *etc.*, (Li *et al.*, 2016). Quercetin offers a variety of potential therapeutic uses primarily in the prevention and the treatment of various conditions. It inhibits production and release of histamine and other allergic substances possibly by stabilizing cell membranes of mast cells (Kempuraj *et al.*, 2006). It inhibits cyclooxygenase, lipoxygenase (Kim *et al.*, 1998) and reactive oxygen and nitrogen species (Knekt *et al.*, 1997). Quercetin intake protects against coronary heart disease (CHD), caused by oxidized LDL. It was also shown to be effective inhibitor of platelets aggregation in dogs and monkeys (Osman *et al.*, 1998). Quercetin suppresses the NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome by affecting these regulators. Quercetin, as an anti-inflammatory, antioxidant and analgesic inflammatory compound, probably has a potential for the treatment of severe inflammation and one of the main life-threatening conditions in patients with COVID-19 (Saeedi-Boroujeni and Mahmoudian-Sani, 2021).

Kidney is one of the target organs for SARS-CoV-2, it is reported that many patients with SARS-CoV-2 infection would develop into acute kidney injury (AKI) (Gu *et al.*, 2021). AKI is associated with high mortality in the clinical setting and contributes to the transition of AKI to chronic kidney disease (CKD). Interestingly, kidney was also identified as the target organ of toxicity for remdesivir, chloroquine and azithromycin (WHO, 2018; Wang *et al.*, 2020a; Usadadia *et al.*, 2020). Moreover, chloroquine leads to endothelial dysfunction due to oxidative stress. The quercetin has been reported to have renal protective effects which may be associated with the blockade of the activation of inflammatory, cell apoptosis-related signaling pathways. Quercetin may also act as SARS-CoV-2 inhibitor by binding with the active sites of SARS-CoV-2 main protease 3CL and ACE2, therefore cut the viral life cycle (Gu *et al.*, 2021). A study reported that quercetin, an antioxidant flavanoid, has efficacy against chloroquin-induced hepatotoxicity (Mishra *et al.*, 2013). It was able to drastically reduce the oxidative stress and hepatotoxicity resulting at higher dosages of chloroquine administration (Mishra *et al.*, 2013). Chloroquine causes endothelial dysfunction due to oxidative stress (Gregório *et al.*, 2021) and it has been documented that quercetin has the potential to revert back the chloroquine-induced toxicity and oxidative stress probably through scavenging the free radical generation (Mishra *et al.*, 2013).

Quercetin has shown the hepatoprotective effects against ritonavir-induced injury to liver through alteration of oxidative stress, inflammation, apoptosis and reversing the tissue degeneration. Quercetin has been observed with attenuating effect against ritonavir-induced Bax, caspase-3, NFκB, and eNOS activation and persuaded

the Bcl2 and pAkt level (Azmi, *et al.*, 2020). Such promising effects favor the therapeutic potential of quercetin in hepatotoxicity and other hepatocellular diseases in COVID-19 patients. Additionally, quercetin can significantly affect the binding of viral S-protein to ACE2 receptor. ACE2 acts as the receptor for the SARS-CoV-2 virus and allows it to infect the cell. Notably, quercetin can also bind to the RBD domain of S-protein, suggesting virus neutralizing effect on SARS-CoV-2 (Pan *et al.*, 2020). In addition to this, quercetin treatment for 4 weeks has been reported to cause marked attenuation of the azithromycin-induced biochemical alterations in serum as well as drug-induced pathological changes in liver and kidney of rats (Usadadia *et al.*, 2020).

The use of protease inhibitors like lopinavir-ritonavir is also characterized by the risk of hypercholesterolemia which can be effectively prevented by treatment of quercetin as quercetin-treated hypercholesterolemic rats exhibited a reasonable improvement of hepatic antioxidant enzymes. Moreover, content of nitric oxide (NO) in serum and liver were markedly decreased in this model (26 and 25%, respectively), and were almost normalized following quercetin administration (Mariee *et al.*, 2012). The major side effect that remains associated with the use of favipiravir is hyperuricaemia for that quercetin may be the ideal agent to prevent kidney damage. The possible mechanism may be inhibition of liver xanthine oxidase by quercetin and improves the ability of clearing free radicals and reduces the lipid peroxidation. Thus, it may play an important role in reducing serum uric acid level and protecting the kidneys (Yao *et al.*, 2011).

3.2 Baicalein (Flavon)

Baicalein is a flavone, originally isolated from the roots of *Scutellaria baicalensis*, *Scutellaria lateriflora* and *Oroxylum indicum* or Indian trumpet flower. Extracts of *S. baicalensis* and its major chemical constituents have been reported to possess antiviral, antitumor, antibacterial, antioxidant, anti-inflammatory, hepatoprotective, and neuroprotective activities (Wang *et al.*, 2018). Several studies showed that the baicalin protects against several types of liver diseases including viral hepatitis, fatty liver disease, xenobiotic induced liver injury with a variety of pharmacological mechanisms (Yang *et al.*, 2021). Baicalein efficiently reduces the gastrointestinal dysfunction caused by ritonavir and plays a role in reducing drug-induced adverse effects (Mehendale *et al.*, 2007). Additionally, baicalein, potently inhibits the replication of SARS-CoV-2. Mechanistically, baicalein inhibits mitochondrial oxidative phosphorylation, and this inhibition is reversibly associated with mitochondrial permeability transition pore activity in host cells (Huang *et al.*, 2020a). Interestingly, oral administration of crystal form β of baicalein caused effective concentration of it against SARS-CoV-2 and it could inhibit SARS-CoV-2-induced injury both *in vitro* and *in vivo* (Song *et al.*, 2021). A study demonstrated the protective effect of baicalein on drug-induced nephrotoxicity and apoptosis by activating the antioxidant defence mechanism in kidneys and down-regulating the inflammatory response (Dai *et al.*, 2017).

3.3 Kaempferol (Flavonoid)

Kaempferol or kaempferol is a secondary plant metabolite and dietary flavonoid found in many common fruits, vegetables and edible plants (*e.g.*, kale, spinach, dill, tea, broccoli, cabbage, beans, tomato, strawberries and grapes) and in medicinal plants, (*e.g.*, *Ginkgo biloba*, *Moringa oleifera*, *etc.*). Green leafy vegetables like spinach and kale, and herbs such as dill and chives are the rich plant sources of

kaempferol. Alone kaempferol is an aglycone form. However, it mostly exists in their glycoside forms after bonding with glucose, rhamnose, galactose, or rutinose. Kaempfero-3-O-glucoside (astragaloside) is a common natural kaempferol glycoside (Calderon-Montano *et al.*, 2011). The type of sugars bonded with aglycone form impacts their bioavailability and bioactivity (Dabeek and Marra, 2019). A wide range of pharmacological properties including antioxidant, anti-inflammatory, anticancer, cardioprotective, neuroprotective, antimicrobial, hepatoprotective, antidiabetic, anti-osteoporotic, estrogenic/antiestrogenic, anxiolytic, analgesic and antiallergic activities has been reported for the kaempferol and its derivatives (Calderon-Montano *et al.*, 2011; Zang *et al.*, 2017). Kaempferol, as a potent antioxidant and anti-inflammatory agent, scavenges free radicals, decreases the formation of reactive oxygen, nitrogen species, inhibits metalloproteinase and modulates endogenous antioxidants and modulates pro-inflammatory enzyme activities (Rajendran *et al.*, 2014; Devi *et al.*, 2015; Silva dos Santos *et al.*, 2021). The strong antioxidant and anti-inflammatory capability of kaempferol can be implicated in the prevention of drug-induced hepatotoxicity, cardiotoxicity and neurotoxicity. Both aglycone and glycoside forms of kaempferol are found to be hepatoprotective in action. In a research finding, kaempferol glycosides isolated from unripe soybean leaves were able to alleviate carbon tetrachloride-induced liver injury in mice owing to its antioxidant properties (Zang *et al.*, 2017). Since, kaempferol is also an inhibitor of p-glycoprotein and CYP3A enzyme (Piao *et al.*, 2008); hence, it could be also used to lower the dose of antiviral anti-COVID drugs which are CYP3A substrate, and thus may reduce the risk of drug-related dose-dependent toxicities. Kaempferol can ameliorate nephrotoxicity (cisplatin-mediated) by modulating oxidative stress, inflammation and apoptosis *via* extracellular-receptor kinases (ERK) proteins and NF- κ B pathway (Wang *et al.*, 2020b). Chloroquine causes endothelial dysfunction due to oxidative stress. The production of excessive reactive oxygen species (ROS) induces endotheliotoxicity and cardiotoxicity. Kaempferol has been documented to have protective effect on vascular endothelium against doxorubicin-induced damage by regulating 14-3-3 γ and ADMA/DDAII/eNOS/NO pathway, inhibiting oxidative stress, and improving mitochondrial function (Wu *et al.*, 2020). Such effect may also be beneficial against drugs cause cardiovascular damage in COVID patients.

In addition to ameliorative effects against toxic effects of COVID-19 drugs, kaempferol may be itself a promising anti-COVID-19 agent. Kaempferol is suggested in the top five ingredients of Chinese medicines which are promising to treat COVID-19 (Huang *et al.*, 2020b). It is postulated that kaempferol may act by targeting on protease protein and inhibiting inflammatory mediators, regulating immunity, and eliminating free radicals. In a molecular docking study undertaken to assess bioactive compounds found in medicinal plants as potential COVID-19 main protease (Mpro) inhibitors, kaempferol has been found to have more affinity than the quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, epicatechin-gallate, zingerol, gingerol, and allicin (Khaerunnisa *et al.*, 2020). Owis *et al.* (2020) reported that kaempferol derivative metabolites isolated from *Salvadora persica* (Miswak) are the promising phytochemicals to act as COVID-19 Mpro inhibitor.

3.4 Curcumin (Polyphenol)

Curcumin, as an active constituent of rhizomes of *Curcuma longa* (turmeric), is a hydrophobic polyphenol (Akbar *et al.*, 2018). Curcumin is used as a spice in daily food and for different purposes such as cosmetic and pharmaceutical industries (Hosseini and Hosseinzadeh, 2018). Curcumin has several pharmacological effects such as antioxidant, anti-inflammatory, anticancer, antibacterial, antiviral, and antidiabetic effects (Babaei *et al.*, 2020).

Curcumin binds to viral S protein and the viral attachment sites of the ACE2 receptor protein to inhibit the entry of SARS-CoV2 (Ho *et al.*, 2021). In addition, curcumin has shown to reduce inflammatory cytokines in COVID-19 patients. In a clinical study with COVID-19 patients, curcumin given as nano-curcumin at 160 mg/day for 14 days reduced the inflammatory cytokines IL-6 and IL-1 β as well as clinical manifestations (fever, cough, dyspnea, headache, chest radiography, lymphocyte, white blood cells, and platelets count) in comparison to placebo-treated group (Valizadeh *et al.*, 2020). Experimental evidences indicate that curcumin exhibits its preventive and curative effect against oxidative stress associated liver diseases through various cellular signaling pathways, *viz.*, ERK/p38/MAPK pathway, hepatic Nrf2/ARE/Keap1 signaling, up regulation of detoxifying genes expression, TIMP signaling, AMPK pathway and lipid metabolism (Farzaei *et al.*, 2018). Growing evidences how that curcumin can reduce chemotherapy, induced toxicity through clearing intra cellular ROS in normal tissues and modulating a series of target molecules such as adhesion molecules, inflammatory factors, transcription and growth factors, apoptosis related proteins and some enzymes and kinases, *etc.* (Liu *et al.*, 2018). Looking to the pharmacological profile of curcumin, it can be used in COVID-19 patients to reduce dose of hepatotoxic antibacterial, antiviral and anti-inflammatory drugs and thereby may reducing adverse effects of allopathic drugs.

3.5 Catechins (Polyphenols)

Catechins are major active constituents of tea leaves and most consumed beverages (tea), second only to water, in many societies of India and abroad. Tea leaves include four major catechins (polyphenolic compound), *i.e.*, epigallocatechin-gallate (EGCG), epigallocatechin (EGC), epicatechin-gallate (ECG) and epicatechin (EC). Catechins derived from tea demonstrate outstanding antioxidant activity due to their ability to neutralize free radicals and boost the detoxification activity of enzymes, including glutathione peroxidase, catalase and glutathione reductase (Sharangi, 2009; Miura *et al.*, 2001). Grzesik *et al.* (2018) reported that catechins have greater antioxidant capacity than glutathione, vitamin C and flavonoids, which attests to their key role in maintaining cellular redox homeostasis. Several authors reported protective effects of catechins for liver, heart and intestine like EGCG may potentially exert a protective effect on the heart muscle in patients undergoing surgery who are susceptible to ischemic injury, by inhibiting the activation of stress-activated protein kinase and signaling pathways inducing the inflammatory response (Kim *et al.*, 2014; Bryk *et al.*, 2014); pre-administration of EGCG (40 mg/kg b.w.) in fluoride intoxicated rats remarkably reversed altered parameters of cardiac tissue like DNA fragmentation, cardiac pro-apoptotic markers, inflammatory markers, anti-apoptotic markers, cardiac troponins, CK-MB, LDH, total cholesterol (TC), triglycerides (TG), phospholipids (PL), free fatty acids (FFA), HDL, LDL, VLDL, heart mitochondrial enzymes (ICDH, SDH, MDH, α -KGDH, NADH dehydrogenase and Ca²⁺ levels), and oxidative stress markers near

normalcy through its antioxidant nature (Miltonprabu and Thangapandiyar, 2015). Catechins supplementation had ameliorated the alcohol-induced liver injury by down-regulating the endotoxin-mediated activation of initial signaling molecule NF- κ B and further going downstream the signaling cascade including tumor necrosis factor- α , nitric oxide and reactive oxygen species and by enhancing the antioxidant profile (Bharrhan *et al.*, 2011). Its pre-treatment showed restoration in the level of cytochrome P450 (CYP) content and in the activities of glutathione metabolizing enzymes, *viz.*, glutathione-S-transferase (GST), glutathione reductase (GR) and glutathione peroxidase (GPx) and other antioxidant enzymes such as, glucose-6-phosphate dehydrogenase (G6-PD), catalase (CAT) and superoxide dismutase (SOD) in both liver and kidney when compared to tamoxifen-treated animals (Parvez *et al.*, 2006). Following intraperitoneal administration of green tea catechins (100 mg/kg) for 7 or 15 days to rats fed the atherogenic diet, significantly higher mean activities of enzymatic and non-enzymatic antioxidants and lower mean levels of MDA in hepatic tissue and lower mean activities of AST, ALT, ALP and LDH in serum were observed, compared to the values in the rats fed the atherogenic diet and treated with saline (Ramesh *et al.*, 2009). Catechin post-treatment significantly attenuated rotenone-induced imbalances in liver; pre-treatment of SD rats with catechin (35 mg/kg b.w. for 21 days) could decrease ketoprofen induced (50 mg/kg b.w. for 1 day) gastric mucosal oxidative damage and could prevent the reduction of GPx, GR antioxidant enzymes, and the GSH/GSSG ratio in the intestinal mucosa (Cheng *et al.*, 2013) and similarly, oral administration of EGCG (2 mg/kg b.w. for 3 days) could decrease indomethacin induced (18 mg/kg b.w. for 4 h) gastric mucosal oxidative damage and prevented the reduction of PG synthesis in the gastric tissues of mice (Adhikary *et al.*, 2013). In addition, epigallocatechin-3-gallate (EGCG) promotes autophagy-dependent survival *via* influencing the balance of mTOR-AMPK pathways upon endoplasmic reticulum stress (Holczer *et al.*, 2018) and EGCG can protect neuronal cells from or attenuate external damage through the autophagy pathway and promoting lysosomal acidification and improving the formation of autophagosomes in the liver (Zhang *et al.*, 2020b). Collectively, catechins possess protective effect on several organs through antioxidant potency and induction of autophagy at molecular level, which can be explored to attenuate several side-effects of COVID-19 drugs.

3.6 Gingerols (Ginger)

Ginger (*Zingiber officinale*) is an important tropical medicinal herb which is being used globally as a spice and also used for healing and therapeutic proposes. Ginger belongs to the Zingiberaceae family in the order Zingiberales and class Monocotyledones (Berg, 1997). Ginger has been reported to have antioxidant, anticancer, anticoagulant, anti-inflammatory and antiemetic action in post-operative vomiting and vomiting during pregnancy. The pungent characteristics of the ginger are due to presence of gingerols and shogaols. Active constituents of ginger, *viz.*, zingerone, gingerdiol, gingerols and shogaols have been reported to have antioxidant activities (Chrubasik *et al.*, 2005). Ginger has shown to produce potent anti-inflammatory effects and ameliorating potential in musculoskeletal and rheumatoid arthritis conditions *via* inhibiting lipoxygenase and cyclooxygenase activities (Srivastava and Mustafa, 1992). Anti-inflammatory potential of ginger in acute and chronic inflammation models was also reported earlier. The effect on acute and chronic inflammation due to inhibition of macrophage activation pathway

(Shimoda *et al.*, 2010). Ginger had also shown to decrease serum levels of C-reactive protein (hs-CRP) and TNF- α in type 2 diabetic patients (Mahluji *et al.*, 2013). Hence, ginger can be considered as a supportive herbal drug to combat the COVID-19 disease severity.

Table 1: Class, mechanism of action, side effects of drugs used in the management of COVID-19

Name of drug	Drug-class	Mechanism of action	Side-effects/toxicities	References
Lopinavir Ritonavir	Protease inhibitors	Inactivating viral proteases to stop viral replication	Hepatotoxicity (increase in AST/ ALT)	Sulkowski <i>et al.</i> , 2000; Nunez, 2006
Lopinavir plus Ritonavir			G.I. events like anorexia, nausea, vomiting, abdominal discomfort, and diarrhea; Acute gastritis	Cao <i>et al.</i> , 2020
			Cutaneous (skin) eruptions, pancreatitis, QT prolongation, CYP3A inhibition, Allergic reaction, asthenia, myalgias, arthralgias, myocardial infarction, seizures, and lactic acidosis	Chandwani and Shuter, 2008
			Hypercholesterolemia, Dyslipidemia	Nolan <i>et al.</i> , 2005
Favipiravir	Nucleotide Analogues	RNA-dependent RNA polymerase (RdRp) inhibitors	Dose-dependent, reversible, and transient hyperuricaemia, QT prolongation	Pilkington <i>et al.</i> , 2020
Remdesivir			Elevated serum uric acid level, Elevated hepatic enzymes, and gastrointestinal symptoms (diarrhoea, nausea, vomiting)	Chen <i>et al.</i> , 2020 Ivashchenko <i>et al.</i> , 2020
			Teratogenicity	Dongyuan <i>et al.</i> , 2020; Pilkington <i>et al.</i> , 2020
			Hepatic enzymes elevation Renal impairment Maculopapular rash Multiple-organ-dysfunction syndrome	WHO, 2018; Grein <i>et al.</i> , 2020 Leegwater <i>et al.</i> , 2020;
			Constipation, hypoalbuminaemia, hypokalaemia, thrombocytopenia, anaemia, and increased total bilirubin	Wang <i>et al.</i> , 2020a
Azithromycin	Macrolide antibiotic	Alters the binding of SARS-CoV-2 virus with ACE2 receptors	Gastrointestinal upset and QTc prolongation	Zuckerman <i>et al.</i> , 2009; Nujic <i>et al.</i> , 2012 Giudicessi <i>et al.</i> , 2013
Chloroquine and Hydroxy-chloroquine	Aminoquinolines	Inhibits the viral entry by inhibiting quinone reductase 2 Inhibit virus replication by inhibiting virus-endosome fusion	Conduction disturbances through altered expression of ion channels Inhibits autophagy Myocardial ischaemia and reperfusion	Louch <i>et al.</i> , 2004; Kwiek <i>et al.</i> , 2004; Yang <i>et al.</i> , 2004; Khan <i>et al.</i> , 2010; Sciarretta <i>et al.</i> , 2018; Mubagwa, 2020; Gevers <i>et al.</i> , 2020
Tocilizumab	Humanized monoclonal antibody	Block IL-6 receptors	Superinfection Mild abnormality in the lipid profile, the liver function test	Chaudhry and Singh, 2020; Somers <i>et al.</i> , 2020

Antiviral drugs are known to produce gastrointestinal side effects including nausea, vomiting and dyspepsia (Neuman *et al.*, 2012). Occurrence of gastrointestinal intolerance is the main factor, which leads to interruption or modification of lopinavir/ritonavir therapeutic regimens (Elzi *et al.*, 2010). Ginger showed positive effects in controlling chemotherapy-induced nausea and vomiting (Mahesh *et*

al., 2005). Ginger administration had significantly ($p < 0.001$) reduced the frequency of mild, moderate and severe nausea and vomiting after antiretroviral therapy (ART) as compared to placebo control group (Dabaghzadeh *et al.*, 2014). Anti-emetic action of ginger is mediated through 5-HT₃ receptor, substance P and acetylcholine receptor antagonism (Marx *et al.*, 2017). Pretreatment with ginger at

1,000 and 2,000 mg/kg dose have been reported to reduce the nausea, tachygastric and plasma vasopressin levels in circular vection induced motion sickness (Lien *et al.*, 2003). The COVID-19 therapeutic drugs such as remdesivir, lopinavir or ritonavir have been reported to induce hepatotoxicity (Zha *et al.*, 2013).

Additionally, the combination of lopinavir and ritonavir in overdose can induce the endoplasmic reticulum stress pathway in the liver and lead to hepatocyte apoptosis and liver damage. In the most advanced stages of COVID-19 infection, there is an increased risk of thrombosis. The use of anticoagulants is also a well-known cause drug-induced liver damage (DILI) (Mahamid *et al.*, 2011). The

hepatoprotective effect of ginger is might be due to its anti-inflammatory and antioxidant activities. Ginger had shown to produce downregulation of transforming growth factor- β 1/Smad3, and nuclear factor-kappa B(NF- κ B)/I κ B signaling pathways, which lead to decrease inflammation and oxidative stress mediated liver damage (Hasan *et al.*, 2016).

Chemical class, chemical name pharmacological properties and ameliorative role of important phytochemicals is also abridged in Table 2. Chemical structure of each phytochemical is depicted in Figure 1.

Table 2: Chemical class, chemical name pharmacological properties and ameliorative role of important phytochemicals

Name and chemical class	Chemical name	Sources	Pharmacological properties and ameliorative role	References
Quercetin (Flavonoid)	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one; dihydrate	Apples, berries, Brassica vegetables, capers, grapes, onions, shallots, tea, and tomatoes, as well as many seeds, nuts, flowers, barks, and leaves	Inhibits production and release of histamine, cyclooxygenase, lipoxygenase, anti-inflammatory, antioxidant, analgesic, renal protective effects, hepatoprotective, reversal of chloroquine-induced toxicity and azithromycin-induced biochemical alterations, inhibition of liver xanthine oxidase	Knekt <i>et al.</i> , 1997; Kempuraj <i>et al.</i> , 2006; Yao <i>et al.</i> , 2011; Mishra <i>et al.</i> , 2013; Usadadia <i>et al.</i> , 2020; Saeedi-Boroujeni and Mahmoudian-Sani, 2021; Gu <i>et al.</i> , 2021
Baicalein (Flavon)	5,6,7-trihydroxy-2-phenylchromen-4-one	Roots of <i>Scutellaria baicalensis</i> and <i>Scutellaria lateriflora</i> , <i>Oroxylum indicum</i> (Indian trumpetflower)	Anti-viral (inhibits the replication of SARS-CoV-2), anti-tumor, anti-bacterial, antioxidant, anti-inflammatory, gastroprotective, hepatoprotective, nephroprotective, and neuroprotective activities	Mehendale <i>et al.</i> , 2007; Dai <i>et al.</i> , 2017; Wang <i>et al.</i> , 2018; Huang <i>et al.</i> , 2020a; Yang <i>et al.</i> , 2021
Kaempferol (Flavonoid)	3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one	Green leafy vegetables, including spinach and kale, and herbs such as dill, chives, and tarragon	Potent anti-oxidant and anti-inflammatory agent	Rajendran <i>et al.</i> , 2014; Devi <i>et al.</i> , 2015; Silva dos Santos <i>et al.</i> , 2021
			Antioxidant, anti-inflammatory, anti-cancer, cardioprotective, neuroprotective, antimicrobial, hepatoprotective, antidiabetic, anti-osteoporotic, estrogenic/ antiestrogenic, anxiolytic, analgesic and antiallergic activities	Calderon-Montano <i>et al.</i> , 2011; Zang <i>et al.</i> , 2017
			Alleviate carbon tetrachloride-induced liver injury in mice model	Zang <i>et al.</i> , 2017
			Ameliorated Cisplatin-mediated nephrotoxicity	Wang <i>et al.</i> , 2020b
			Protective effect on vascular endothelium against doxorubicin-induced damage	Wu <i>et al.</i> , 2020
Curcumin (Polyphenol)	(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione	Turmeric (<i>Curcuma longa</i>)	Antioxidant, anti-inflammatory, anticancer, antibacterial, antiviral, and antidiabetic effects, inhibit the entry of SARS-CoV2, reduce inflammatory cytokines	Farzaei <i>et al.</i> , 2018; Babaei <i>et al.</i> , 2020; Valizadeh <i>et al.</i> , 2020; Ho <i>et al.</i> , 2021

Catechins (Polyphenols)	(2R,3S)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol	<i>Camellia sinensis</i> , tea, apples, persimmons, cacao, grapes, and berries	Antioxidant activity, inhibiting the activation of stress-activated protein kinase and signaling pathways of inflammatory response, induction of autophagy	Parvez <i>et al.</i> , 2006; Sharangi, 2009; Bharrhan <i>et al.</i> , 2011; Bryk <i>et al.</i> , 2014; Kim <i>et al.</i> , 2014; Zhang <i>et al.</i> , 2020b
Gingerols (Ginger)	5-hydroxy-1-(4-hydroxy-3-methoxyphenyl) decan-3-one	Ginger (<i>Zingiber officinale</i> Roscoe)	Anti-inflammatory effects, Reduction in musculoskeletal and rheumatoid arthritis pain via inhibiting lipoxygenase and cyclooxygenase activities, Decrease serum levels of C-reactive protein (hs-CRP) and TNF- α , Control of chemotherapy-induced nausea and vomiting, Anti-emetic action by inhibition of 5-HT ₃ receptor, substance P and acetylcholine receptor activities, Antioxidant and hepatoprotective effect via down regulation of transforming growth factor- β 1/Smad3, and nuclear factor-kappa B (NF- κ B) /I κ B signaling pathways	Srivastava and Mustafa, 1992; Mahesh <i>et al.</i> , 2005; Mahluji <i>et al.</i> , 2013; Hasan <i>et al.</i> , 2016; Marx <i>et al.</i> , 2017

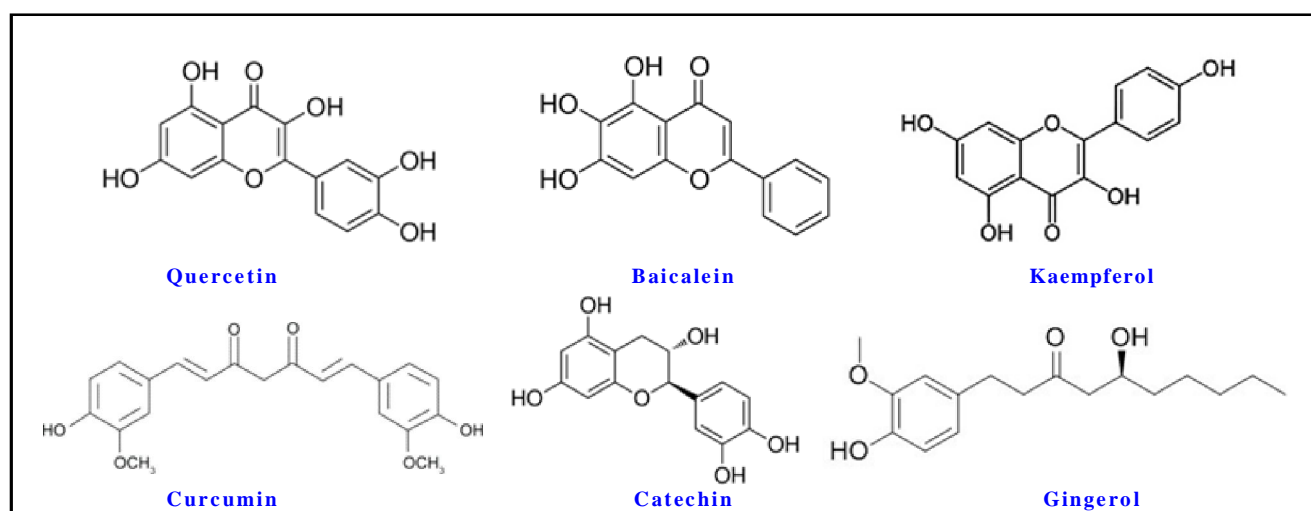


Figure 1: Chemical structures of important phytochemicals.

4. Conclusion

Complications and higher level of pathogenesis may be responsible for side effects of drugs used or recommended for the management of COVID-19. Various phytochemicals like quercetin, baicalein, kaempferol, curcumin, catechins and gingerols may be useful to ameliorate the side effects of drugs. Further, research efforts are required to explore the drug-herb interaction and the ameliorating potential of such phytochemicals against COVID-19 drugs.

Disclaimer

Compilation of the information related to possible ameliorating potential of phytochemicals against side effects of commonly used drugs in COVID-19 is useful to strengthen the knowledge of scientific personnel who are working in the field of research. The information collected herewith can not be used for diagnosis and therapeutic purpose.

Conflict of interest

The authors declare that there are no conflicts of interest relevant to this article.

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Citation

Priti D. Vihol, Rasesh D. Varia, Ratn Deep Singh, Jatin H. Patel, Harshad B. Patel, Sarita Devi and Urvesh D. Patel (2021). Ameliorative potential of phytochemicals against side effects of COVID-19 drugs: A review. *Ann. Phytomed.*, Volume10, Special Issue1 (COVID-19): S51-S64. <http://dx.doi.org/10.21276/ap.covid19.2021.10.1.6>