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REVIEW ARTICLE

The Use of Plant Steroids in Viral Disease Treatments: Current Status and Future Perspectives

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ABSTRACT

Plants have been used for the prevention and treatment of diseases since the early days of humankind and constitute the natural sources of today's modern medicine. Approximately one-quarter of approved drugs are derived from plants. Plant steroids are a group of biologically active secondary metabolites with a 5α and 5β gonane carbon skeleton. There is immense chemical diversity in plant steroids due to the side chains, oxidation status of the carbons in the tetracyclic core, and methyl groups. Plant steroids are classified into several groups based on their biological functions and structures, also on their mechanism of biosynthesis. All subtypes have been investigated for their anti-cancer, immunomodulatory, anti-inflammatory, and anti-viral properties. The novel coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2), which carries an RNA genome. An intense effort has been made in terms of effective treatment strategies and vaccine development since it was declared a pandemic. Nucleoside analogs such as favipiravir and remdesivir are used to block RNA-dependent RNA polymerase enzymes. Other strategies including neuraminidase inhibitors, chloroquine, and hydroxychloroquine as immunomodulatory agents, stem cell and cytokine based therapies are being conducted. One part of the therapies against SARS-CoV-2 is focused on the spike (S) protein of the virus that binds to the host receptor, angiotensin-converting enzyme 2 (ACE2). It has been suggested that SARS-CoV-2 S protein has a free fatty acid-binding pocket, and according to molecular simulations, steroids are ligands that bind to this pocket. Therefore, this review summarizes the plant steroid biological actions as well as their anti-viral potential against SARS-CoV-2 infection.

Keywords: Plant steroids, anti-viral drug, SARS-CoV-2

INTRODUCTION

PLANT STEROIDS AND THEIR BIOLOGICAL ACTIONS

Plant steroids are unique compounds found throughout the plant kingdom, which exert critical physiological effects including plant growth, development, and reproduction. They are also important micronutrients commonly found in a diet[1]. Plant steroids have a definite chemical structure composed of four carbon rings called the steroid nucleus (Figure 1). The nucleus typically contains the tetracyclic 5α or 5β-gonane carbon skeleton with methyl substituents at C-10, C-13, and an alkyl side chain at C-17 (Figure 1).

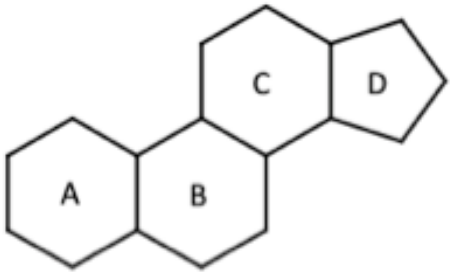


Figure 1. Plant steroids backbone structure. Created by ChemSpider.

Plant steroids are quite similar to those of well-known an-

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imal steroids in terms of the regulation of the expression of specific genes and complex physiological processes involved in cell growth and division. The addition of distinct chemical groups at different positions to the nucleus leads to the formation of many types of steroids categorized into seven main groups based on their biological functions, structures, and taxonomic considerations such as brassinosteroids, bufadienolides, cardenolides, cucurbitacins, ecdysteroids, saponins, steroidal alkaloids, and withanolides (Table 1).[2,3]

Table 1. Major groups of plant steroids.

Plant steroid group	Examples
Phytosterols	β-Sitosterol , campesterol , stigmasterol
Brassinosteroids	Brassinolide , castasterone
Withanolides (withasteroids)	Withanolide A ,withanolides Q
Phytoecdysteroids	20-Hydroxyecdysone
Steroidal alkaloids /glycoalkaloids	Jervine , α-solanine , conessine
Steroidal saponins /sapogenins	Tigogenin,25-Epi-ruizgenin
Mammalian steroidal hormones	Androstenone , progesterone
Bufadienolides	19-nor bufadienolides
Cardenolides	Quabain
Cucurbitacins	Cucurbitacins(A,B,C,D)
Ecdysteroids	Dacryhainansterone

Along with their important physiological functions within plants, they exhibit pharmacological activities helpful to humankind. Due to the knowledge about the pharmacological activities of these herbs, they are gaining increasing attention all over the world as herbal medicine supplements.[4] The pharmacological actions of these various types of plant steroids indicated that they have growth-promoting, cardiotonic, antimicrobial, anti-tumor, hepatoprotective, anti-fungal, antioxidant, antiinflammatory, and anti-viral roles.[5–8]

Brassinosteroids

One of the most studied classes of plant steroids is brassinosteroids (BRs). BRs were discovered in 1979 by Grove et al. and have been isolated from the pollen of *Brassica napus*.[9] The most bioactive BR was referred to as brassinolide, followed by castasterone (CS) among more than fifty brassinosteroids identified to date.[10] BRs regulate growth in very low concentrations in plants and have the ability to make impacts on physiological processes (germination, growth, reproductive development, etc), modulation of the antioxidative enzyme cascade and protection from various stress conditions, including drought, heavy metals, herbicidal injury, thermotolerance, and salinity.[11,12] Antigenotoxicity effect of 24-epibrassinolide has been verified employing Allium cepa chromosomal aberration assay.[13] *In vitro* analyses in neuronal PC12 mammalian cell line demonstrated that the potent antioxidant and neuroprotective role of 24-epibrassinolide reduce DNA fragmentation, Bax/Bcl-2 protein rate and cleaved caspase-3 and inhibit the MPP^+-induced (1-methyl-4-phenylpyridinium) apoptosis in dopaminergic neurons.[14] BRs have numerous impacts on plant physiological processes including germination, growth, reproductive development, and protection from environmental stresses including drought, heavy metals, and salinity.[15] For instance, 24-epibrassinolide (EBR) has been shown to increase thermotolerance of tomato plants via heat-shock proteins.[16] BRs, apart from their well-known roles in the improvement in quality and yield of crops, have been shown to inhibit cancer cell survival and replication of viruses. 28-homocastasterone(homoCS) and EBR were first suggested as nuclear hormone receptor blockers and to cause cell cycle arrest in prostate and breast cancer cells. Recently, Coskun et al showed that EBR can trigger mitochondria-mediated apoptosis in an endoplasmic reticulum stress-inducing manner in prostate and colon cancer cell lines without causing the same effect in normal epithelial cells due to the autophagic induction.[17] Their findings showed that calreticulin alteration, an ER-resident chaperone protein, was the main phenomenon in EBR-induced apoptosis. The anti-angiogenic roles of BRs were also identified. Both EBR and homoCS inhibited the proliferation, adhesion, and migration of HMEC- 1HUVEC endothelial cells.[18,19] BRs were shown to be effective against several disorders apart from cancer, e.g., Alzheimer's and Huntington's Diseases, sexual differentiation disorders, steroid-induced osteoporosis and cataract, hyperadrenocorticism, etc.[20]

Bufadienolides

Plant steroid subgroups, bufadienolides, and cardenolides, are described as cardiac glycosides because they increase the contractile force of the heart via the inhibition of cardiac Na^+-K^+/ATPase.[21,22] They consist of a steroid nucleus bearing a pentadienolide ring at C17β. Bufadienolides and cardenolides containing plants can cause severe toxicity to livestock. Besides, they have a wide range of bioactivities including blood pressure stimulating, immunoregulatory, etc.[23] They also exert cytotoxic effects on HCT116 colon, A549 lung, and HepG2 hepatocellular, A-375a skin, MCF-7 breast cancer cell lines.[23,24] Bufadienolides and cardenolides are also found in other organisms such as *Bufo marinus* and *Chrysolina coerulans*, Lampyridae, and Colubridae as well as mammalian tissues.[24]

Cucurbitacins

Cucurbitacins are steroid-like molecules found in the plants of the Cucurbitaceae family, as well as Cruciferae, Rubiaceae, etc. They possess a lanostane skeleton with hydroxy, methyl, and oxo substituents with unsaturation at positions 5 and 23 Their medicinal and toxic properties have been identified. Cer-

tain species-rich in cucurbitacins have been used in traditional medicines against metabolic diseases like diabetes via activating the 5' AMP-activated protein kinase pathway.[25] The anti-tumor, anti-inflammatory, antidiabetic, and immunosuppressant roles of these metabolites were investigated in several studies. The anti-cancer effect of cucurbitacins, such as elatericin A and B, was discovered more than fifty years ago via inhibition of cell proliferation, induction of apoptosis *in vitro*, and tumor growth in tumor-bearing mice. Oi et al cited cucurbitacin as a signal transducer activator of transcription 3 (STAT3 inhibitor and a novel therapeutic agent in osteosarcoma, lung, laryngeal, and breast cancer cell lines.[25,26] Cucurbitacins can inhibit the expression of tumor necrosis factor (TNF) and proinflammatory mediators such as cyclooxygenase-2 to exert an anti-inflammatory effect.[27]

Phytoecdysteroids

The natural polyhydroxylated plant steroids group, phytoecdysteroids, appears in many plants as toxins for protection against herbivore insects. More than 300 different phytoecdysteroids have been described, and they show a wide distribution in the plant kingdom.[28] Besides, their presence is not restricted to plants, several aquatic plants and fungi also contain ecdysteroids.[29] A broad spectrum of these compounds with medicinal properties in mammals has been described, including antimicrobial, hepatoprotective, hypoglycemic, and hypocholesterolemic. The ecdysteroids have very low toxicity in mice with LD50 approximately 6 g kg^{-1} of body mass.[30,31] They have been suggested as skin collagenase inhibitors and accelerators of wound healing. More recently, ecdysteroids isolated from *Vitex doniana* have exhibited antidepressant effect via monoaminergic transmission interference in mice studied by Isohola et al. Besides, the antioxidant and antiproliferative action of phytoecdysteroids have been also reported both *in vitro* and *in vivo* studies.[32,33] The fact that ecdysteroids influence various cellular processes was explained by their Akt/Protein kinase B signaling targeting.[30]

Saponins

Saponins are a group of plant steroids with a classical steroid nucleus to which sugar groups are attached. They are subdivided into triterpenoid and steroid glycosides. Saponins are used in many applications in the pharmaceutical industry as a starting material for the synthesis of steroidal hormones such as vitamin D and cardioactive glycosides. They are also used as food additives or firefighting foams due to their foaming and surface tension reducing properties,[34] in other words, they are natural surfactants and emulsifiers. Saponins have been proposed for the treatment of diabetes, obesity, and osteoporosis.[35] Their anti-inflammatory, hypocholesterolemic, and immune-stimulating roles are also described. They have been suggested as anti-cancer agents because of their ability to inhibit cell proliferation, angiogenesis, oxidative stress and promote apoptosis[36,37] in a variety of cancer cells in vitro including brain, breast, colon, pancreas, prostate, and ovary without causing toxicity and changes and body weight in rats, mice, and rabbits.[38–40]

Steroidal Alkaloids

Steroidal alkaloids (SAs) are a diverse class of plant steroids with a steroid nucleus containing nitrogen atoms attached to a ring or side chains.[41] Some examples of steroidal alkaloids are α solanine, solamargine, tomatidine, solasonine, α-solanine, briofilin, and α-chaconine with anti-cancer activity[42] *via* induction of either intrinsic or extrinsic pathways of apoptosis.[43,44] The cell cycle arrest and anti-metastatic effect of some SAs have been also reported. Solanidine and spirosolane types are also known to possess pregnane skeleton and exhibit anti-fungal and anti-viral roles.[45] Antifungal, antiviral, antitumor and embryotoxic activities of steroidal alkaloid glycosides (spirosolane and solanidine) have been proven via various spectroscopic analyses.[46,47] Recently, both in *vitro* and *in vivo* investigation on *Sarcococca saligna*, the hepatoprotective and immunosuppressive potential of isolated SAs was defined. According to the results in a dose-dependent treatment, human T-cells proliferation, IL-2 production and phytohemagglutinin stimulated T-cell proliferation have been suppressed on a significant scale.[48]

Withanolides

Withanolides are steroidal lactones carrying oxidized C22 and C26 ergostane skeleton and have been found to show immunomodulatory, anti-inflammatory, and anti-microbial activities by altering NF-κB and JAK/STAT signaling. Therefore, their application in inflammation-mediated chronic diseases has been studied in several studies. Besides, like other plant steroids, withanolides showed antitumor activity in several cancer cell lines for example, the most potent withanolide, withaferin A caused cell cycle arrest in MCF-7, SUM159, and SK-BR-3 breast cancer cell lines.[49] Withaferin A exhibited an antiproliferative effect in melanoma, head and neck squamous cell carcinoma, and human glioblastoma by altering Akt/mTOR and MAPK signaling pathways. Another important effect is that withanolides can target breast cancer stem cells by decreasing mammospheres and aldehyde dehydrogenase activity.[50–52]

Phytosterols

Phytosterols (plant sterols) are a ubiquitous group of plant steroids. Phytosterols (PS), a member of the triterpene family, are steroidal alcohols. They are known as natural plant metabolites that exhibit functional similarity with sterol-structured cholesterol in mammalian cells. Unlike cholesterol, they are

not synthesized endogenously in the human body. More than 250 phytosterols of dietary origin such as legumes, fruits, vegetables, tubers, beans, nuts, wheat germ, whole grains, sunflower seeds and vegetable oil have been defined. Among them, campesterol, β-Sitosterol, and stigmasterol are the most sterols present in edible fats of PSs. Sterols and stanols both in PSs represent a class of sterol composites that modulate essential physiological functions such as membrane fluidity, permeability and signal transduction in plant cells. While sterols are in "free" unbound form, they can be covalently bonded through their ester or glycosidic bonds additionally.[53–55] Various studies emphasize that phytosterol glucosides are critical in the functional organization of plasma membrane lipid rafts, plasma membrane enzymes and receptor proteins. PSs also act as precursors in the synthesis of main bioactive compounds such as steroidal glycoalkaloids, steroidal saponins, phytoecdysteroids, and brassinosteroids.[2,56,57] As a new functional food group, extensive research has been conducted on the anticancer, antidiabetes, anti-obesity, cytotoxic, insecticidal/larvicidal, antiatherosclerosis, anti- Alzheimer and hepatoprotective effects of PSs related to the management of human health and metabolic disorders.[57] Plant sterols have been proven to increase mitochondrial ATP content, reduce dyslipidemia, insulin resistance and dysfunction of cells, improve gut microbiota dysbiosis and barrier dysfunction, increase adipose inflammatory signal, reduce oxidative stress, and modulate inflammatory signals. The fact that PSs interact directly and / or indirectly with free radicals and specific proteins in redox signaling pathways involved in various physiological processes is actually thought to be due to their antioxidant properties.[58] Ergosterol, campesterol, β-sitosterol, and stigmasterol, inhibit the production of inflammatory enzymes and pro-inflammatory cytokines in different cell lines. In LPS-stimulated HaCaT human keratinocytes and J774A.1 mouse macrophages, TNF-α, interleukin (IL)-8, IL-1β and IL-6 secretion have been reduced after the application of β-sitosterol isolated from moringa oleifera.[59] Scientific evidence reveals that PSs modulate the gut microbiota composition and play a protective role against pathologies. In addition, functionality has a beneficial effect on gut inflammation and barrier integrity. *In vitro* faeces analysis of morbidly obese individuals during the fermentation process determined that sterol supplementation decreased the population of *Erysipelotrichaceae*, a family of bacteria associated with lipidemic imbalances.[60] The same microbial changes have been confirmed in mouse and hamster models of hypercholesterolaemia.[61]

ANTI-VIRAL ACTIVITIES OF PLANT STEROIDS

Due to the inevitable reality of viral infection risks, modern medical science aims to prevent the transmission and spread of viral infection and also to minimize the treatment and financial burden. In this regard, scientific research and pharmaceutical companies have been examining their potential compounds for the identification and production of new antivirals. Most plants have hormonal functionality and are considered to be steroid synthesis factories. Recent research proves that although there is a structural distinction of plant steroids, they have a viral transcription/replication alteration effect, along with their inhibitory, antioxidant, and immunomodulatory activities, support host defense mechanisms and cell survival in the event of viral infection.[62,63] With the known details of the preventive role of functional foods and medicine herbs with natural nutraceutical ingredients such as polyphenols, terpenoids, flavonoids, alkaloids, sterols in noncommunicable diseases (NCDs), their preventive and / or therapeutic roles associated with the immune system in viral infectious diseases (CDs) in particular remain a mystery in many respects.[63,64]

In a recent study, 4 biomarker extracts of *Guiera senegalensis*, a phytoestrol family were examined against hepatitis B virus in HuH7 liver cell lines, and their antioxidative, antiviral and hepatoprotective potential have been confirmed.[65] Molecular investigations of β-sitosterol as a common phytosterol in Chinese traditional medicine have been designed in influenza (IAV) infected mouse models in a dose dependent manner β-sitosterol (150–450 υg/mL) that is able to suppress inflammation *via* p38 mitogen-activated protein kinase (MAPK) and NF-κB signaling. Additionally, RIG-I signaling, harmful IFN production and acute lung injury inhibition have been reported.[66]

Activation of the resistance mechanisms of BRs against DNA and RNA viruses is the main characteristic of their defense strategies. As a result of the host cell's special sensors (PRRs) encountering with expressed structural motifs (PAMPs) unique to the pathogen virus, immune response mechanisms that inactivate bacteria, viruses, fungi and oomycetes are triggered.[20,67,68] Recent studies indicated that brassinosteroids and their derivatives inhibited the in vitro replication of herpes simplex type 1 (HSV-1) thymidine kinase (TK)+ and TK- strains, and the arenaviruses Junin (agent of Argentine hemorrhagic fever), Pichinde, and Tacaribe viruses.[69] The structural alterations determine their efficacy on antiviral responses through increasing host recognition mechanisms. BR treatment in tobacco plants substantially reduced *Tobacco mosaic virus* (TMV) viral infection and increased crop yields by 56% with induced resistance to TMV.[70] The exogenous application of brassinolides to *Nicotiana benthamiana*, was shown as an antiviral mechanism during TMV infection. Brassinosteroids could activate different cellular targets such as MEK2 (MAPKK)-SIPK (salicylic acid-induced protein kinase) and RBOHB (respiratory burst oxidase homolog protein B)-dependent ROS burst. Additional targets such as BES1/BZR1 could inhibit RBOHB dependent ROS generation and maintain growth function as a hallmark of plant immunity.[20]

In a case study, it was shown that the *Arabidopsis thaliana* plant belonging to the cruciferous family, BAK1 and/or BKK1 proteins in the steroid signaling are mandatory to maintain plant

immunity against RNA viruses' infection such as Turnip crinkle virus (TCV).[71] Enhancement of antioxidative enzymatic performance and gene expression regulation have been observed *in A. thaliana* infected with cucumber mosaic virus (CMV) after BR treatment.[72] Shamsabadipour et al. determined the structural properties of triterpene and steroid compounds obtained from *E. denticulate* plant endemic to Iran by NMR and mass spectroscopic approaches. Toxicity and antiviral analysis results proved that both types of compounds have protective effects against Herpes Simplex Type 1 (HSV-1) virus infection.[73]

The anti-viral activity of bufadienolides and cardenolides has been reviewed by Kamano et al. Buadienolide derivatives showed selective inhibition of Rhinovirus at very low concentrations. In addition, bufadienolides isolated from Kalanchoe pinnata were shown to inhibit the activation of Epstein Barr virus.[74] Besides, a potential anti-bovine viral diarrhoea virus (BVDV) activity of nine members of cucurbitacins was found. In addition, some of the members, namely cucurbitacin B, D and E, have been shown to inhibit Hepatitis C replicon replication in HuH-7 cells.[75,76]

Tomatidine in green tomatoes is a steroidal alkaloid with enzymatic activity. An in vitro research focused on antiviral reaction of tomatidine versus Chikungunya virus (CHIKV), highlighting the strong controlling role of this compound on CHIKV replication processes and a significant decrease in the count of infected cells both early or post infection.[77] The quest for effective anti-PEDV drugs to control the swine epidemic diarrhea virus (PEDV), defined by the fatal diarrhea symptom in piglets, continues. Wang and colleagues, by designing *in silico* and in vitro assays, draws attention to the inhibitory role of tomatidine during PEDV replication cycle by targeting the 3CL protease in IPEC-J2 and Vero cell lines. Findings suggest that tomatidine has an antiviral activity against porcine reproductive and respiratory syndrome virus (PRRSV), infectious gastroenteritis virus (TGEV), seneca virus A (SVA), and encephalomyocarditis virus (EMCV) strongly.[78]

SARS-CoV-2 AND COVID-19

Coronavirus family members (CoVs), which cause respiratory infections of human beings and other mammals, represent an enveloped and large group of single-stranded RNA viruses. Since the genome of these viruses can be directly translated into viral proteins by the host cell's ribosomes, they are defined as positive-sense viruses (viral mRNA). It is known that CoVs belong to the Nidovirales family including Roniviridae, Arteriviridae, Coronaviridae and Mesoniviridae main four members.[79–81] Phylogenetic analysis disclosed that the viral genome ranging from 27–32 kb has 29.903 nucleotides and shows 89.1% nucleotide similarity with SARS-like coronaviruses.[82,83] The viral ORF1ab gene encodes the envelope glycoprotein or spike protein (S), membrane (M) protein, nucleocapsid (N) protein, and envelope (E) proteins, which are defined as structural proteins.[84] Follow-up of clinical reports reveals that coronavirus members, SARS-CoV, SARS-CoV-2 and MERSCoV, show the potential to infect mammals, causing very serious symptoms. The SARS-CoV-2 virus is the seventh in this regard.[85] SARS-CoV-2 was raised in December 2019 in China from an unidentified zoonotic source, which might be generated from pangolin or bat coronaviruses. The disease is characterized by hypoxemic respiratory failure, which requires air-ventilation support at the severe stages of the disease. COVID-19 patients can also show asymptomatic or mild symptoms of the disease such as fever, dry cough, fatigue, lung failure mainly acute respiratory distress syndrome (ARDS), and cytokine storm at the very late stage of the disease. Until now, different candidates have been suggested for therapy including novel or repurposed antibodies, anti-inflammatory drugs, and corticosteroids.The World Health Organization (WHO) guidelines that were published in September 2020 recommend the systemic corticosteroids rather than no corticosteroids for the treatment of patients with severe and critical COVID-19 who required mechanical ventilation.[86] On the other hand, the same guideline also indicated not to use corticosteroids in the treatment of patients with non-severe which was based on certainty evidence. Conversely, guidelines from the Infectious Diseases Society of America that were published in April 2020 issued a weak recommendation against corticosteroids, except for patients with COVID-19 and ARDS treated in the context of a clinical trial.[86]

While early observational data from China suggested a potential mortality benefit of corticosteroids in COVID-19, previous studies of corticosteroids in other viral pneumonia, especially severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), found an association with delayed viral clearance and reinforced concerns that corticosteroids may impair host response to SARS-CoV-2. Furthermore, a meta-analysis of observational studies suggested increased mortality with corticosteroid treatment in influenza pneumonia. As the COVID-19 pandemic spread across the world, clinicians struggled to weigh the potential benefits of corticosteroids against the many potential harms associated with these drugs. Despite being overwhelmed with critically ill patients, multiple clinical trial groups around the world launched high-quality RCTs of corticosteroids for severe COVID-19. Additionally, recognizing the urgency of aggregating data from these trials to guide management, WHO coordinated a prospective meta-analysis of these ongoing RCTs (PROSPERO CRD42020197242). The clinical trial groups agreed to share data, even before acceptance of their trial data for primary publication. With a press released on June 16, 2020, reporting the results of the UK-based RECOVERY trial, the existing approach for treating and studying patients with COVID-19 underwent a major change. In this large open-label randomized trial enrolling 6425 patients (2104 randomized to

receive dexamethasone and 4321 randomized to receive usual care), treatment with dexamethasone (6 mg/d for 10 days) reduced mortality by one-third in patients receiving mechanical ventilation (29.3% vs 41.4%, respectively; rate ratio, 0.64 [95% CI,0.51-0.81]) and by one-fifth in patients receiving supplemental oxygen (23.3% vs 26.2%, respectively;0.82 [95% CI, 0.72-0.94]) compared with usual care alone.[13] However, there was no benefit among patients not receiving respiratory support (1.19 [95% CI, 0.91-1.55]), and the possibility of harm could not be excluded.[86]

Potential Effects of Plant Steroids as Natural Therapeutics Against Coronaviruses

With the lack of a specific/successful drug in the treatment of SARS-CoV-2 infection, most researchers focus on the antiviral effects of phytomedicines against SARS coronaviruses simultaneously. In the process defined as the term 'molecular farming', plants' secondary metabolites are preferred in the production of alternative drugs and recombinant vaccines, since they exhibit fewer side effects compared to allopathic drugs.[87,88]

Drug design studies are mainly focused on S protein RBD (receptor binding region) region of SARS-CoV-2, which targets angiotensin converting enzyme 2 (ACE2) receptors for the initial attachment process.[89,90] Understanding the lipid rafts and lipid-activated molecular troughs in the plasma membrane areas that support the entry of the SARS-CoV-2 virus into the host cell (endocytosis) and infection suggests valuable clues to the emergence of powerful antiviral strategies.[91]

Recent studies on lipophilic naturally derived phytosterols emphasize that these substances interact with lipid rafts, destabilize the structure of membrane cholesterol and impress biochemical activities associated with lipid rafts.[92] Experimental research on *Lycoris radiata* has shown that four herbal steroidal alkaloids derived from this plant may be candidates for the development of anti-SARS-CoV therapeutics.[93] In an *in vitro* study targeting the anti-coronaviral activity and mechanisms of action of saicosaponins (A, B2, C and D), it has been proven that saicosaponin B2 significantly inhibits human coronavirus 229E infection by interfering with viral absorption and replication processes.[94] Research results examining the antiviral properties and therapeutic potential of cardenolides and bufadienolides against SARS-CoV-2, HCoV-229E and HCoV-OC43 belonging to the coronavirus family report that these steroid compounds are the remarkable inhibitors of selected coronaviruses.[95]

Very recent comprehensive *in silico* analysis on the interaction between various plant secondary metabolites (4,704 ligands) and the four structural target proteins of SARS-CoV-2 reveals in detail the possible physicochemical, bioavailability, and binding energy scores during interaction. The virtual screening and molecular docking results demonstrate that the steroidal lactones, triterpene sterols, coagulins, steroidal saponins, triterpene glycosides, triterpene saponins and steroidal glycoalkaloids were similar, showing lower and favorable binding energy scores against the target amino acid residues of the S protein.[96] Molecular Simulation approach using the University of Bristol Insertion Engine recommends steroids, vitamins, retinoids as ligands that bind the free fatty acid pocket of SARS-CoV-2 S Protein.[97]

The pathophysiology of COVID-19 is complex as various signaling pathways and molecules are involved in the inflammatory state. SARS-CoV-2 initiates pro-IL-1 secretion, inflammation and IL-1 beta hyper activation and up-regulation by binding to toll-like receptors. This hyperactive proinflammatory response is described as Cytokine Storm (CS). The severity of the infection that has occurred is marked by the levels of circulating cytokines and chemokines (monocyte chemotactic protein1, IL-2, IL-6, IFNγ, TNF). Cytokine Storm (CS) is known to cause severe fibrosis induction in the lung tissues of infected patients, which can result in death unfortunately.[98,99] Obtained results of *in vitro* and *in vivo* studies focusing on the anti-inflammatory properties of Cucurbitacin against viral infections prove that Cucurbitacin II B decreased the expression of IFNγ, TNFα and IL-6. In addition, Cucurbitacin E and R, respectively, downregulate IL-1 and TNFα expression by suppressing NF-κB translocation and the STAT3 signaling pathways.[100,101]

CONCLUSION

Viral diseases are very common in spreading, like in the case of COVID-19, and become pandemic. To treat or prevent viral infections is a challenge since it is usually impossible to control the replicative cycle of the virus without interfering the host one, or to estimate the mutations that it will carry after each replicative cycle. Plant steroids are divided in to several subclasses, and some of them have been shown as good candidates to treat viral infections since they have few side effects to the host. The exemplary studies described above indicate that plant steroid family members have a high potential for clinical efficacy, especially against SARS-CoV-2 infection. It is thought that the pharmacological manipulation of these compounds may show promising results in the course of the pandemic including COVID-19.

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