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TRITERPENOIDS AS POTENTIAL CANDIDATES FOR TREATMENT OF COVID -19 AND RESPIRATORY DISORDERS

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ABSTRACT

COVID-19 outbreak has emerged as most dangerous threat across the globe wrecking populations and economies since December 2019. It is a burning topic worldwide that has become a big challenge for the scientists and researchers to find a solution for this deadly disease. Although, there is plenty of literature supporting the effectiveness of herbs in treating viral infections but it is somewhat difficult to predict how well particular herbs perform as in most cases they are administered with allopathic medications. While scientists still struggle for claiming the efficacy, recommendation of unproved and clinically untested molecules by health authorities merely based on available data can be misleading and potentially dangerous. Well, a few preventive measures can be advised but not treatment advice until the potential drugs are screened for their pharmacological activity against COVID-19. This Review explores a certain group of phytochemicals- triterpenes from natural godowns and their possible efficacy against respiratory viral infections to serve as potential drugs for treatment of SARS-CoV-2 as we await the development and testing of specific anti-viral drugs.

Keywords: Triterpenoids, COVID- 19, SARS- severe acute respiratory syndrome, potential leads

OVERVIEW

A new type of coronavirus has been identified recently and named 2019 novel coronavirus (COVID-19) by the World Health Organization (WHO). It has taken the world to toll, causing an increasing rate of pneumonia cases since late December 2019. COVID Infections were first identified in Wuhan, China, before being detected in other Chinese cities and in more than a dozen countries around the world by early February 2020. WHO on 30 January 2020, declared the outbreak as Public Health Emergency of International Concern? COVID-19- infected pneumonia is characterized by flu-like symptoms including cough, Fever, severe acute respiratory distress syndrome, and in some cases death. Further, Human to-human transmission has been confirmed for the virus, which is considered related to severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS). Like MERS-CoV and SARS-CoV, the COVID-19 is a serious threat to human health. This pandemic requires effective prevention and treatment **[1]**. Earlier also in late 2002, severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) caused the first major pandemic of the new millennium. Coronaviruses are well known to undergo genetic recombination leading to new genotypes and outbreaks. The culture of eating exotic mammals in southern China along with the presence of a large reservoir of SARS-CoV-like viruses in horseshoe bats, has already been referred to as a time bomb. The possibility of the reemergence of SARS and other novel viruses from animals or laboratories has been very well predicted long back **[2]**.

After the COVID-19 outbreak, a mortality of just 0.1% was reported in Guangdong, of infected people - compared with Wuhan's rate of 2.6% - and none of the confirmed patients in Zhejiang had died. The patients in Guangdong and Zhejiang were being given herbal drinks to relieve symptoms even before they were testing positive. The Institute of China based on *in-vitro* research in laboratories, discovered Shuanghuanglian oral liquid that could be used to inhibit the 2019-nCoV **[3]**. In the absence of any cure available for this pandemic, application of traditional Chinese medicine in treatment of SARS-CoV-2 is largely inspired by treatment of SARS caused by outbreak of SARS coronavirus (SARS-CoV) in 2002 in Guangdong province of China **[4]**. SARS-COV-2 is structurally like SARS-COV and hence the mechanism of action of SARS-COV-2 in the host cell may

be comparable to SARS-COV. Indian medicinal plants can be considered likely to be potential drugs for treatment of COVID-19 **[5]**.

Triterpenoids (TTs) are widely distributed class of secondary metabolites in the plant kingdom and due to their potent anti-viral activity, they can be explored in finding a new drug leads with TT nucleus targeting HCoVs **[6]**. The need of the hour is to search new and more powerful antiviral agents to prevent, treat or retard viral infections. Extensive clinical research on TT molecules having anti-viral activity may pave a gateway for treating the current pandemic **[7]**. TTs are a class of plant metabolites with high structural diversity and they may provide important sources of lead compounds in drug research and development as they generally show no or weak toxicity. However, the value of TTs in preventing and treating viral diseases has only partially been exploited **[8]**. Certain TTs isolated from plants have reported to show anti-viral activities, such as arjunolic acid, cucurbitacin, glycerrhizic acid, gymnemic acid. Further these compounds can be exploited for their activity in SARS **[9]**. Also reports suggest antiviral activity of certain TT compounds against respiratory syncytial virus (RSV) **[10]**. Let us explore in detail the various TTs for their anti-viral activity through this review.

PATHOGENESIS & SYMPTOMS OF COVID-19

Before we discuss the potential molecules for treatment of COVID-19, it is important to know the pathogenesis.

During the initial, 1-2 days of infection, the inhaled virus SARS-CoV-2 binds to epithelial cells in the nasal cavity and begins replication **[11]**. For both SARS-CoV2 and SARS-CoV, ACE2 is the main receptor. At this stage, there is local propagation of the virus but a limited innate immune response and virus can be detected by nasal swabs. Even if the viral burden in this stage may be low, these individuals are infectious. The RT-PCR value for the viral RNA might be useful to predict the viral load and the nasal swab samples might be more sensitive than throat swabs.

Further in next few days, a more significant immune response is triggered following the propagation and migration of the virus down the respiratory tract along the conducting airways. Nasal swabs or sputum should yield the virus (SARS-CoV-2) as well as early markers of the innate immune response and the disease COVID-19 is clinically manifested **[12]**. The level of CXCL10 (or some other innate response

cytokine) may be predictive of the subsequent clinical course as CXCL10 has also been reported to be useful as disease marker in SARS. In about 80% of the patients with COVID-19, the disease will be mild and mostly restricted to the upper and conducting airways. Hence, these patients may be monitored at home with conservative symptomatic therapy.

About 20% of the infected patients will progress to stage 3 disease and will develop pulmonary infiltrates and in some cases, it may be more severe remarkably with age. In this stage, the virus reaches the gas exchange units of the lung and infects alveolar type II cells like SARS-CoV and influenza viruses. As, SARS-CoV propagates within type II cells, large number of viral are released, and the cells undergo apoptosis and eventually die. Further SARS and COVID-19 lead to diffuse alveolar damage with fibrin rich hyaline membranes and a few multinucleated giant cells. Both papain-like protease (PLpro) and SARS-CoV-2 main protease (Mpro) are key viral cysteine proteases essential for the viral replication inside the host cell, where cause activation of the replication complex that in turn initiate the viral RNA replication. Hence, the recovery will require a robust innate and acquired immune response with epithelial regeneration **[13]**.

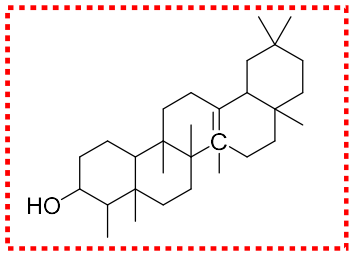
Further patients infected with COVID-19 showed abnormal respiratory findings, higher leukocyte numbers, and increased levels of plasma pro-inflammatory cytokines. The laboratory studies of infected persons showed leucopenia with leukocyte counts of 2.91 × 10^9 cells/L of which 70.0% were neutrophils and a value of 16.16 mg/L of blood C-reactive protein was noted which is above the normal range (0–10 mg/L). High erythrocyte sedimentation rate and D-dimer were also reported. Other symptoms observed were severe pneumonia, RNAaemia, combined with the incidence of ground-glass opacities and acute cardiac injury Significantly high blood levels of cytokines and chemokines were noted in patients with COVID-19 infection that included IL7, IL1-β, IL1RA, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA. Some of the severe cases showed high levels of pro-inflammatory cytokines including IL2, IL7, IL10, IP10, MCP1, MIP1α, GCSF and TNFα that promote disease severity.

TRITERPENOIDS SHOWING ANTIVIRAL ACTIVITY

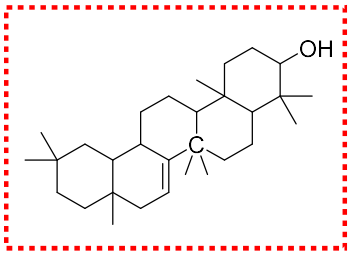
The various triterpenoids (TTs) which exhibit antiviral activities and can serve as potential drug molecules for treatment of COVID-19 are enlisted in **Table 1 and Figure 1**.

Table 1: Triterpenoids which are reported to have activity against SARS-CoV species

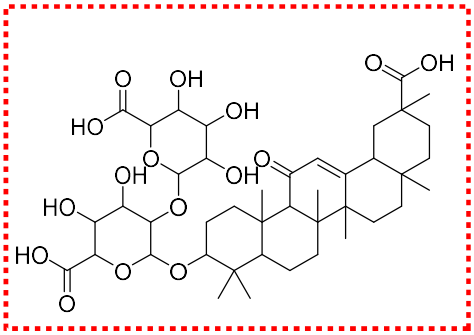
S. No.	Triterpenoids	Activity/Mechanism of action	Reference
1.	3-β-friedelanol & Epitaraxerol	Anti-Human CoV	[14]
2.	Glycyrrhizin and its derivative-α-hedrin, Betulonic acid	Anti- SARS-CoV	[15]
3.	Arjunolic acid, Cucurbitacin, Glycerrhizic acid, Gymnemic acid	Broad spectrum anti-viral activity	[16]
4.	Glycyrrhizin	Respiratory syncytial virus (RSV)	[17]
5.	Lupane - type triterpenes	Anti- SARS-CoV	[18]
6.	3-oxobetulinic acid & 11-oxoursolic acid	Broad spectrum antiviral activity	[19]
7.	Betulinic acid and its derivatives	Competitive inhibitors of SARS-CoV	[20}
8.	Oleanane triterpenes	Inhibitory activity against (Porcine epidemic diarrhea virus) PDEV- Coronavirus	[21]
9.	Betulinic acid	Possible inhibition of SARS-CoV	[22]
10.	Glycyrrhizin	Inhibition of replication of SARS-CoV	[23]
11.	Glycyrrhizic acid derivatives	anti-SARS-CoV	[24]
12.	Corosolic acid and Glycyrrhizin	Direct binding to both host cell target ACE2 receptor and viral target main protease of CoV	[25]
13	Oleanic acid	Possible anti -SARS- CoV acitivity	
14	Ginsenoside- Rb1	Anti- SARS-CoV activity	[26]
15	Saikosaponins	*In-vitro* anti-human coronavirus 229E activity	[27]
16	Methyl tanshionate, sugiol and α-Cadinol	Main protease (Mpro) inhibition from SARS-CoV Virus	[25]
17	8-β-hydroxyabieta-9, 13-dien-12-one, Dehydroabieta-7-one and Tanshinone I	Papain- like protease -2 (PLpro)inhibition from SARS-CoV Virus	
18	1β-hydroxyaleuritolic acid	Inhibition of SARS-CoV-2 main protease (Mpro) and papain-like protease (PLpro) Reverse transcriptase inhibitor	[26]
19	β-Aescin, quinone-methide triterpenes	Inhibition of NF- ƙB activation and cytokines production. Inhibition of the replication of SARS-CoV-1 in vitro	
20	Oleanolic acid, Ursolic acid and Hederagenin	Activity against replication of SARS-CoV-1	[27]



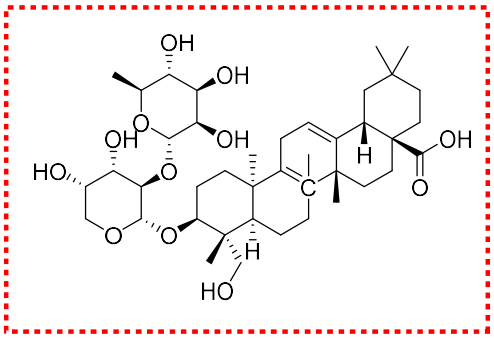
3-beta-friedelanol



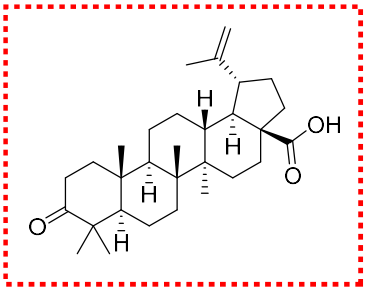
Epitaraxerol



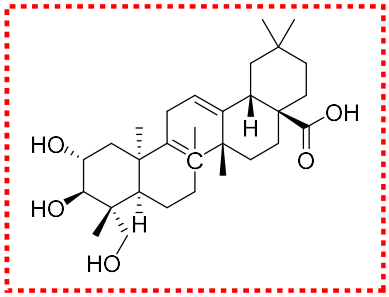
Glycyrrhizin



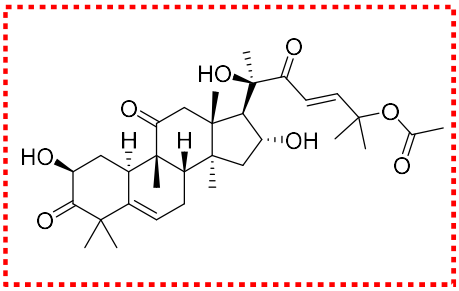
alpha-hedrin



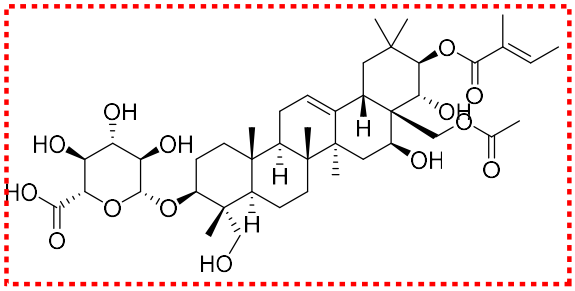
Betulonic acid



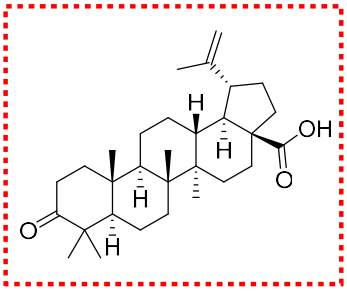
Arjunolic acid



Cucurbitacin



Gymnemic acid



3-oxobetulinic acid

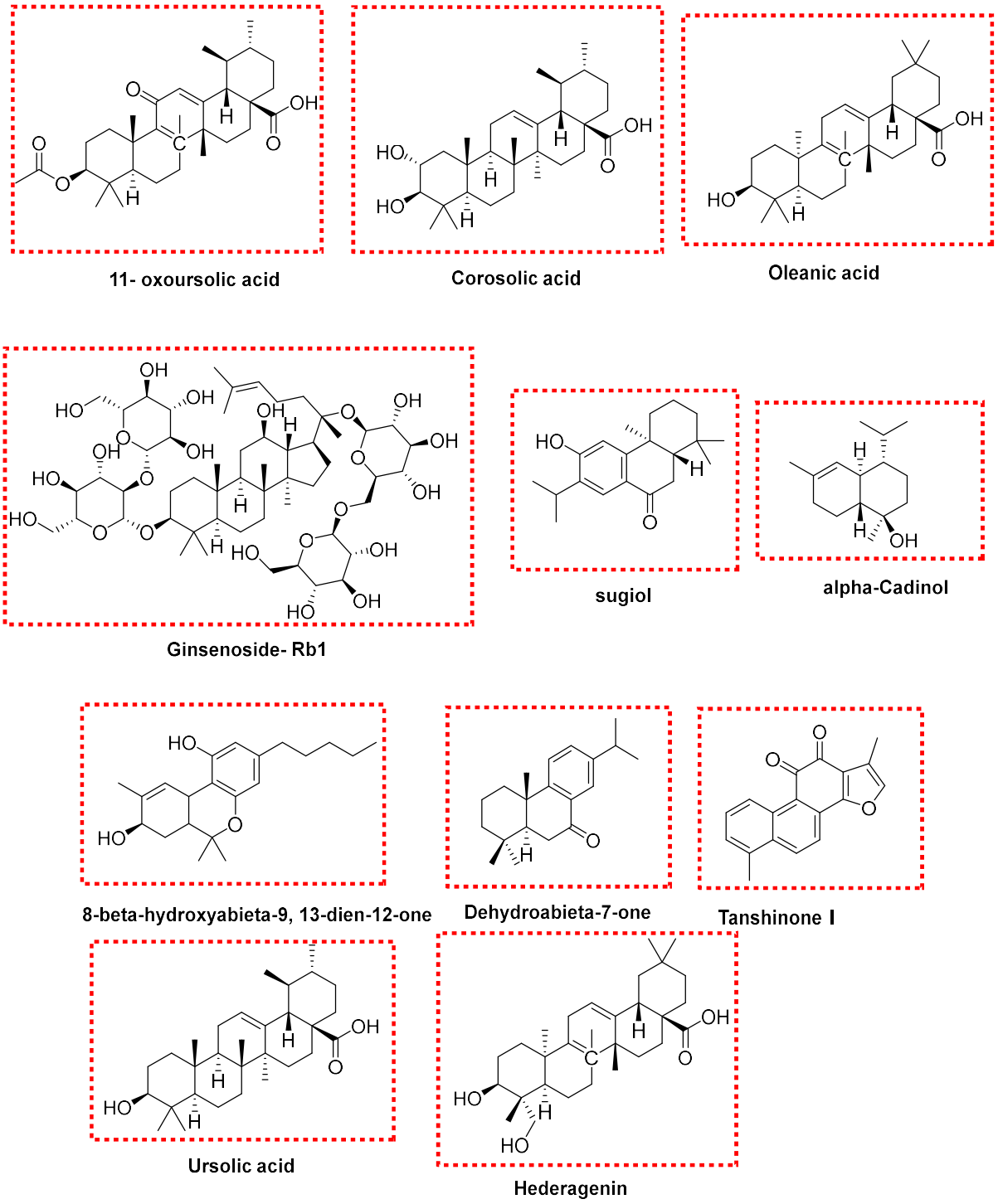


Figure 1: Triterpenoids which are reported to have activity against SARS-CoV species

CONCLUSION & FUTURE PROSPECTS

Going through the available literature and researches on triterpenoids, it can be concluded that they possess immense pharmacological potential. Glycyrrhizin, betulinic acid, 8-β-hydroxyabieta-9, 13-dien-12-one and ginsenosides may be subjected to extensive research for their potential efficacy in COVID- 19. Although there is no significant data on cucurbitacin against SARS-CoV, but they may be explored for their possible activity in SARS. Plants like *Glycerrhiza glabra, Momordica charantia* and *Quillaia saponaria* containing triterpenoid saponins may be exploited for their potential activity against SARS as saponins may provide promising leads for treating this pandemic. Staunch research on these medicinal leads from the nature may prove to be of immense significance in generating scientific validated data regarding their efficacy in COVID- 19.

Conflict of Interest

The authors have no conflict of interest.

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