Journal of Molecular and Pharmaceutical Sciences

Review

Exploring the possible use of saponins in the treatments of COVID-19

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Abstract

A new coronavirus called severe acute respiratory syndrome (SARS-CoV-2) appeared in Wuhan (China) on 2019 and became a pandemic owing to its rapid emergence. Until now, there is no effective treatment to fight against this disease. The plants continuously gave effective phytoconstituents with low toxicity. Saponins are a class of plants secondary metabolites that have shown good efficacy in several studies against several viruses. Some of them was attracted attention of Scientifics in the treatment of COVID-19. The purpose of our review is to examine the use of saponins during the pandemic in the treatment of SARS-CoV-2, notably the antiviral activity. The literature search was executed using PubMed database to search for suitable keywords such as COVID-19, saponins for articles published till 20 August 2021.

The present systematic review was performed based on PRISMA protocol. Data extraction and quality evaluation of articles were performed by three reviewers. 41 articles were the results of the search and based on the inclusions and exclusions criteria, 15 articles were included in this systematic review. Firstly, we focused on the in vitro and vivo studies. Glycyrrhizin, Escin, Esculentoside A and Saikosaponins have already been shown to be effective against certain coronaviruses. Platycodin D, Ginsenoside Rg6 and Oleanolic acid derivatives tested against SARS-CoV-2 and showed a good activity. In the second part of this systematic review, we anticipated in summarizing on the in-silico studies, especialy the computational molecular docking simulations of saponins against differents sets of SARS-CoV-2 binding protein. In-silico study revealed that, Saikosaponin-U, Saikosaponin-V, glycyrrhizin and Esculentoside A have good Molecular docking simulations.

Keywords:

SARS-CoV-2, COVID-19, saponins, antiviral, docking.

*Received October 07, 2023; accepted December 10, 2023

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Cited as: Bouchachoua L, Mameri F, Bekhouche K, Djakoun A. Exploring the possible use of saponins in the treatments of COVID-19. J. Mol. Pharm. Sci. 02 (02), 2023, 10-28.

1. Introduction

On December 2019, The world saw the emergence of an epidemic of pneumonia caused by novel Severe Acute Respiratory Syndrome-coronavirus 2 (SARS-CoV-2), novel positive-strand RNA coronavirus enveloped like other coronaviruses well-known (CoV) such as, Acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV) [1]. On January 7, 2021 according to World Health Organization (WHO), the total number of people infected has reached over 87 million and deaths worldwide have exceeded 1 million. COVID-19 kills approximately 3.02% [2].

SARS-CoV-2 consists of a spike protein (S), a membrane protein (M), an envelope protein (E) and a nucleocapsid (N)[1], it enters the host cell through viral binding to the S-glycoprotein of the angiotensin 2 converting enzyme (ACE2) [3]. Usually COVID-19 is transmitted by inhalation or by contact with droplets or contact surfaces contaminated by them, then by touching the nose, mouth or eyes. Although aerosolization / fecal-oral transmission is also supposed[4]. Patients with COVID-19 often present with symptoms such as fever, cough, nasal congestion, fatigue, headache and diarrhea. Severe forms have been reported such as lymphopenia, dyspnea and symptoms lungs corresponding to pneumonia [4]. SARS-CoV-2 is considered to share 79.5% of the SARS-CoV genetic sequence which we can then learn from research and clinical experience with SARS-CoV for manage SARSCoV-2 pneumonia (COVID-19) [5].

Herbal medicines and their secondary metabolites have received a lot of attention in the treatment of COVID-19. Saponins are high molecular weight glycosides [6]. Moreover, they are secondary metabolites synthesized by many different plant species [7], but also by certain marine organisms and insects [8]. Saponins derived from the Latin word "*sapo*" meaning soap. In water, saponins molecules give stable foams [7]. They have a bitter taste, hemolytic activity, detergent properties and are toxic to fish (piscicide) [6]. Chemically saponins are glycosylated compounds made up of two parts: a water-soluble carbohydrate chain called a glycone and a fat-soluble structure called an aglycone[8]. According to the structure of the aglycone part, saponins are classified into two classes: steroidal and triterpene saponins. The third group in the saponins family is attributed to heterosides of steroidal amines. However, other authors distinguish this group as alkaloids [9]. Aglycones are normally C-3 hydroxylated and some methyl groups are frequently oxidized to hydroxymethyl, aldehyde or carboxyl function[6] . The sugar moiety is linked to the aglycone through a glycosidic ester or ether bond at one or two glycosylation sites [23]. The molecule is called monodesmosidic saponin when the oligosaccharide chain is attached at the C3 position, while bidesmosidic saponins have two sugar chains, often with one attached by a C-3 ether bond and one attached by an ester bond (acyl glycoside) in C-28 (triterpene saponins)as shown in Fig. 1, or an ether bond in C-26 (furostanolsaponins) [6]. The constituent sugars of the most common saponins found are: L-arabinose, D-xylose, D-glucose, D-glucuronic acid, D-galactose, Lrhamnose and D-fructose.

Since the publication of Kofler's book Die Saponine in 1927, great interest has been shown in their characterization and in the study of their pharmacological and biological properties[6]. Indeed they have many activities, the most important being 1) The permeabilization of the cell membrane, 2) The reduction of the cholesterol level in the blood,3) Stimulation of the secretion of the luteinizing hormone which leads to abortive properties,4) Immune capacity by interaction cytokines, 5) Cytostatic and cytotoxic effects on malignant tumor cells, 6) Immunostimulating properties make them usable as adjuvants for vaccines,7) Synergistic improvement in immunotoxicity [8]. Moreover, they have antiviral properties because they can interact with viral envelope and capsid protein, resulting in disruption of viral particles. It can also interact with the host cell membrane which inhibits the attachment of viral particles to host cells, thus preventing fusion by coating the cell surface, which minimizes the spread of infections [10].

This work aimed to discuss the anti-SARS-CoV-2 potential of this chemical class through the analysis of tests performed against several human coronaviruses.

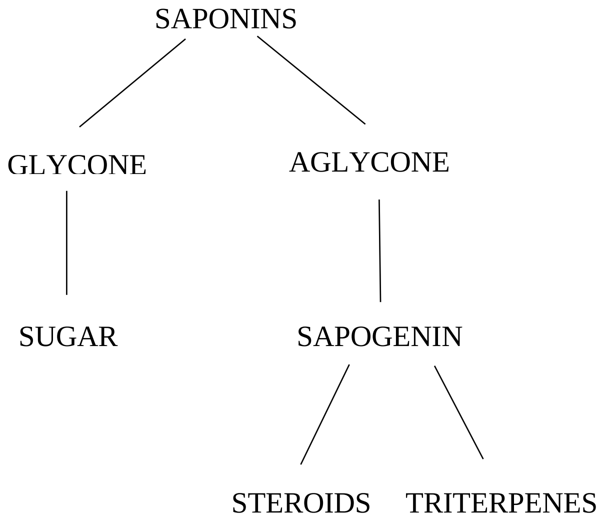


Fig. 1. Composition of saponins

2. Methods

The existing systematic review is accomplished and reported in conjunction with preferred reporting items for systematic reviews andmeta-analyses (PRISMA) guidelines [11].As represented in Fig .2.

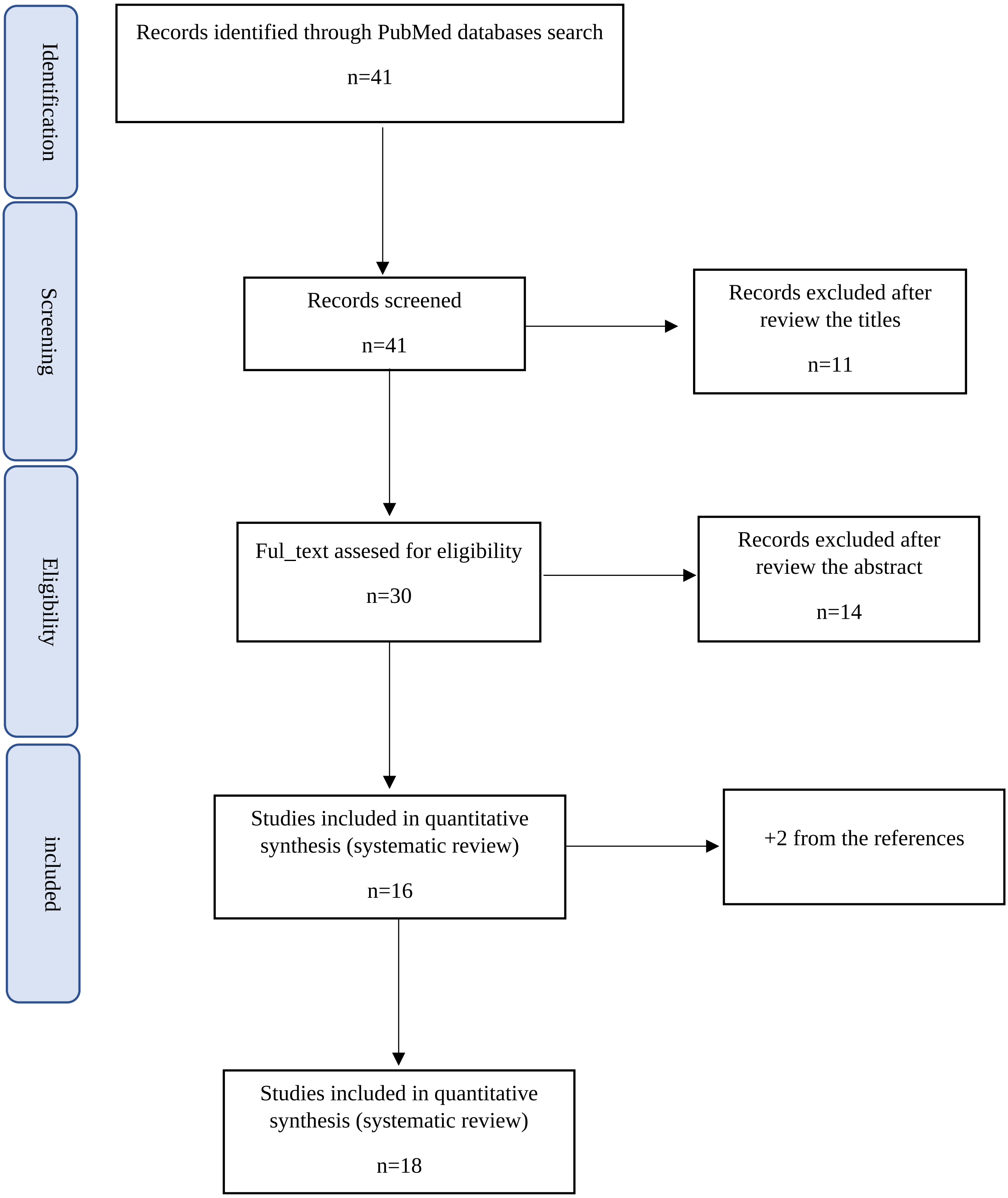


Fig .2. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

2.1. Search strategy and selection criterea

Among the (41) records that were identified through electronic searching using PubMed database to search for the mains keywords such as: saponins, covid 19, date of publication until August 20th 2021, removed 25 studies that did not meet the inclusion criteria, selected 16 potentially relevant reports that were identified and retrieved for detailed evaluation.

2.2. Data extraction

Data from articles were extracted independently by three reviewers to fill in table items.

2.3. Included studies

The studies reviewed in this systematic review were about the saponins used us antiviral agents against SARS-CoV and SARS-CoV-2 including in vitro, in vivo and in silico investigations.

2.4. Excluded studies

The studies excluded from this article were the articles which talked about the use of saponins as adjuvants in vaccines, other articles are excluded because they talked about saponins without focusing on the antiviral proprieties.

2.5. Quality assessment

Quality of each publication was evaluated by three independent reviewers. This review addressed the potential of saponins against SARS-CoV and SARS-CoV-2.

2.6. Statistical analysis

It was not possible to conduct a meta-analysis because there were not enough proper research studies on this subject.

3. Results

3.1. In vitro and in vivo studies

Tab.1 antiviral proprieties of saponins against SARS-CoV and SARS-CoV-2

Molecules	Type	Plant name	Virus	Cell model	IC50/EC50/concentration	Ref	Antiviral/anti-inflammatory activities
Glycyrrhizin (**1**)	Triterpenoide saponin	Glycyrhiza globa	SARS-CoV (FFM-1 FFM-2)	Vero cells	EC50=600mg/mL adsorption EC50=300mg/mL penetration EC50=2400mg/mL replication	[12]–[14]	Antiviral
			SARS-CoV	Vero-E6 cells	EC50 > 400 µg/mL		
			SARS- CoV	Vero cells	EC50=365 µM		
Escin(**2**)	Triterpenoide saponin	Aesculus trippocastanum	SARS-CoV	Vero E6	EC50=6.0 µM	[4]	Antiviral
Platycodine D (**3**)	Triterpenoide saponin	Platycodon grandiflorum	SARS-CoV-2	H1299 cells	IC50 : 0.72 µM	[15]	Antiviral
				HEK293T cells	IC50 : 0.69 µM		
Saikosaponin A (**5a**)	Triterpenoide saponin	Bupleurum falcatum L	Human coronavirus	HCoV-229E	IC50=8.6 ± 0.3 µM	[16]	Antiviral
Saikosaponin B2 (**5b**)					IC50=1.7 ± 0.1 µM		
Saikosaponin C (**5c**)					IC50=19.9 ± 0.1 µM		
Saikosaponin D (**5d**)					IC50=13.2 ± 0.3 µM		

N- {3b-O- [2, 4-di-O-(a-L-rhamnopyranosyl)-b-Dglucopyranosyl]-olean-12-en-28-oyl}-benzylamine (**7**)	Triterpenoide saponin	Hémi-Synthetic	SARS-CoV-2	293T-ACE2	IC50= 4.37 µM	[1]	Antiviral
Ginsenoside Rg6 (**4**)	Steroidal saponin	Panax ginseng	SARS-CoV-2	PBMCs C57BL/6 mice, ICR mice	50 µg/mL 5 mg/kg	[17]	Anti-inflammatory
Esculentoside A (**6**)	Triterpenoide saponin	Phytolacca esculenta	HCoV-OC43	HCT-8 cells	+	[3]	Antiviral

3.2. In silico study

Tab.2 Molecular docking score and binding free energy for the protein–ligand complexes of saponins

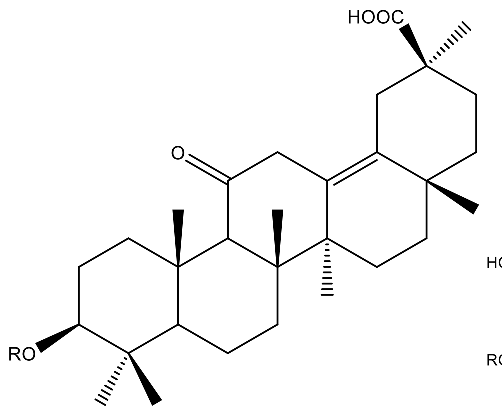
Molecules	PDB:ID	Proteins	Residues	N° interactive residues in protein H-Bond	Score fonction	Score binding (Kcal/mol)	Ref.
Esculentoside A (**6**)	6LZG	S-protein	Gly496, Gly502, Tyr476 Asn501, Thr500, Ala475 Asn487, Lys417, Gln498 Phe456, Tyr489, Tyr453 Leu455, Gln493	14	AutoDock Vina	- 13.1	[3]
	6M0J		Asn501, Gly502, Tyr505, Thr500, Lys417, Tyr449, Gly446, Gln493, Gln498, Tyr453,	17			

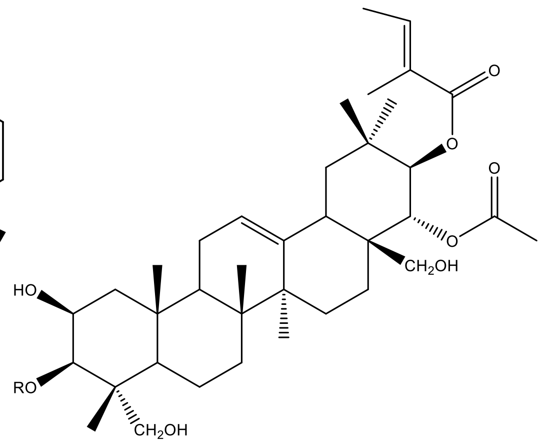
			Phe456, Leu455, Tyr489, Phe486, Asn487, Gly496, Ala475			The best docking score	
	6VW1		Tyr489, Ala475, Phe456, Tyr453, Gln498, Gln493, Asn501, Thr500, Leu455 Gly476, Tyr449, Asn487, Tyr505, Gly502, Gly496, Phe486	16			
			Phe486, Phe456, Asn487				
	7A94		Gly502, Gly476, Ala475 Tyr505, Asn501, Leu455 Gln498, Gln493, Thr500	12			
	6XR8-1R42		Phe490, Tyr489, Arg403, Asn487, Phe486, Gly485, Gly476, Gly502, Ser477, Thr478, Gln498, Tyr505, Gly496, Asn501, Tyr449, Asn450, Ser494, Leu452, Tyr453, Leu455, Gln493	21			
Saikosaponin-A (**5a**)	6LU7	Main protease	His41, Glu166, Arg188, Gln189, Thr190, Gln192	6	AutoDock Vina v.1.0.2	-8.8	[18]
	1R4L		Ala348, Glu402, Arg514, Tyr515, Arg518	5		-11	
	6W01	NSP15	-	-	SchrodingerMaestro 2018-1 MM	-4.725	[19]
	6VSB	S-protein	-	-		- 5.143	

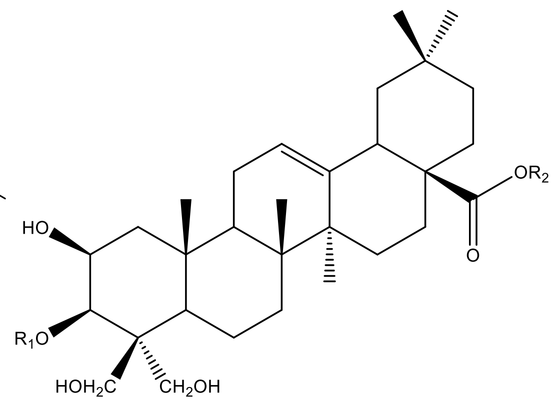
Saikosaponin-V (**5e**)	6W01	NSP15	Glu 234, Asn 278, Pro 344, Val 292, Tyr 343, Leu 346, Glu 340, Gln 245	8	SchrodingerMaestro 2018-1 MM	-8.358	[19]
	6VSB	S-protein	Phe 346, Ser 402, Thr 460, Ile 475, Asp 459, Thr 461, Phe 403, Gly 298	8		-8.299	
	IN26	Human interleukin-6 receptor	-	-	Schrödinger maestro 2018-1 MM	- 7.077	[20]
Saikosaponin-U (**5f**)	6W01	NSP15	Glu 234, Asn 278, Pro 344, Val 292, Tyr 343, Leu 346, Glu 340, Gln 245	8	Schrödinger maestro 2018-1 MM	-8.358	[19]
	6VSB	S-protein	Phe 346, Ser 402, Asn 271, Glu 257, Asp 345	5		-8.429	
	1N26	Human interleukin-6 receptor	-	-	Schrödinger maestro 2018-1 MM	- 6.987	[20]
Saikosaponin-C (**5c**)	6W01	NSP15	Lys 290, Gln 245, Hip 235, Thr 341, Asn 278, Leu 346	6	Schrödinger maestro 2018-1 MM	-6.981	[19]
	6VSB	S-protein	Phe 403, Asp 345, Lys 341, Glu 372	4		-7.274	

	5O0X	NADPH-Oxidase 5 (NOX5)	-	-	Schrödinger maestro 2018-1 MM	- 9.202	[20]
Saikosaponin- B2 (**5b**)	6W01	NSP15	-	-	SchrodingerMaestro 2018-1 MM	-4.697	[19]
	6VSB	S-protein	-	-		-6.19	
Saikosaponin-D (**5d**)	6W01	NSP15	-	-	SchrodingerMaestro 2018-1 MM	-3.738	[19]
	6VSB	S-protein	-	-		-5.638	
3-*O*-*β*-D-glucopyranosyl-spinasterol (**11**)	6LU7	M^{pro}	Thr 199, Asr 289, Arg 131 Asr 197, Lys 137	5	PyRx 0.9.4 virtual screenig software	–7.13	[21]
3-*O*-*β*-D-glucopyranosyl-oleanolic acid (**8**)			Thr 199, Asn 238, Lys 137	3		–7.29	
lucyoside F			Leu 272, Thr 199, Asr 289	3		–7.47	

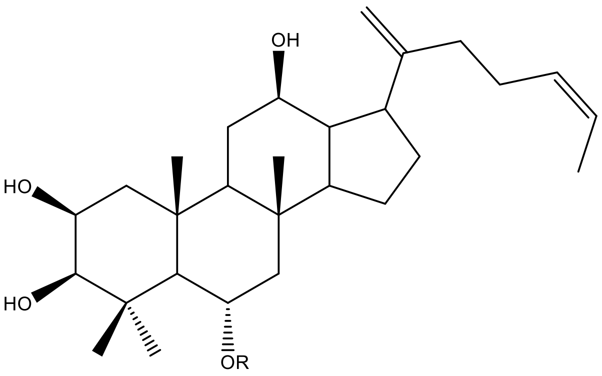
(**9**)							
lucyoside H (**10**)			Lys 137, Leu 287, Ala 285, Met 276, Asn 277	5		–7.54	
Glycyrrhizin (**1**)	-	S-protein	ARG-559, GLN-388, ARG-393, ASP-30	4	-	-9	[16]
	6LU7	Main protease	Phe140, His163, His164, Arg188	4	AutoDock Vina v.1.0.2	-8,9	[18]
	1R4L		Arg273, His345, Thr365, Thr371, Tyr515, Arg518	4		-9,9	



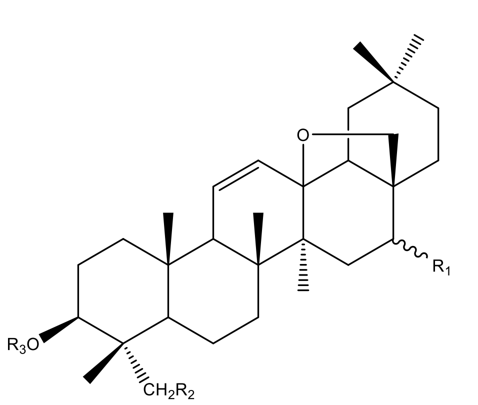




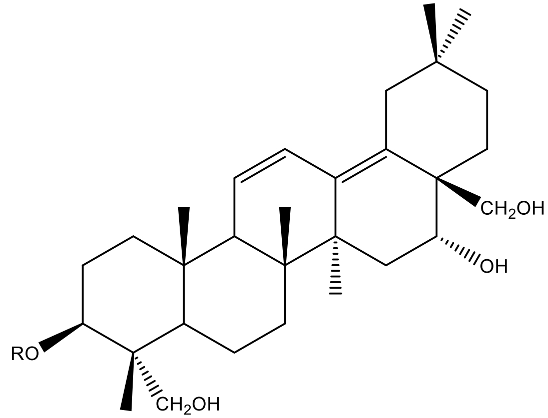
	R	
1	-β-D-GluA-(1→2)-β-D-GluA	
	R	
2	-β-D-Glu-(1→2)-[β-D-Gal-(1→4)]-β-D-GluA	
	$\mathbf{R_1}$	$\mathbf{R_2}$
3	-β-D-Glu	-β-D-Api(1→3)--β-D-Xyl(1→4)-α-L-Rha-(1→2)-α-L-Ara



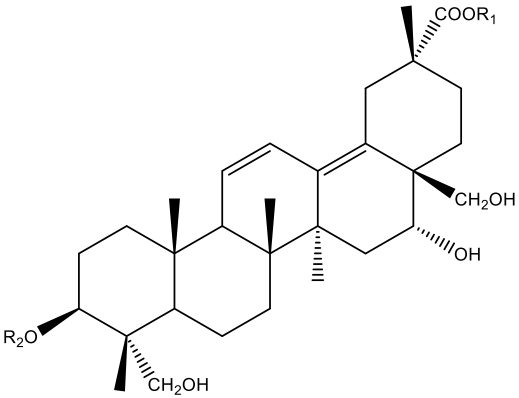
	R
4	-α-l-Rha-(1→2)-β-D-Glu



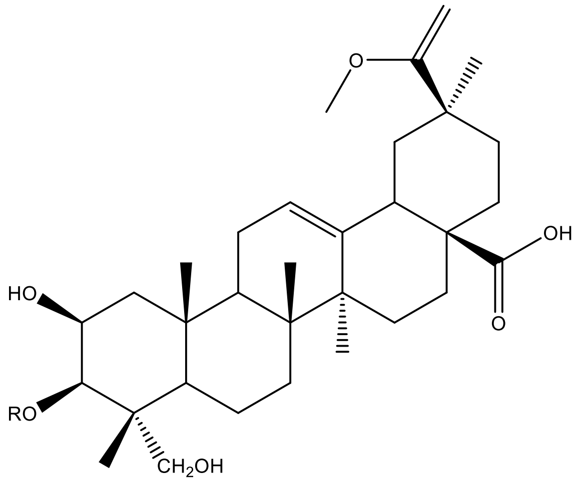
	R_1	R_2	R_3
5a	-β-OH	OH	-β-D-Glu-(1→3)-D-Fuc
5c	-β-OH	H	-β-D-Glu-(1→6)-[α-L-Rha-(1→4)]-β-D-Glu
5d	-α-OH	OH	-β-D-Glu-(1→3)-β-D-Fuc



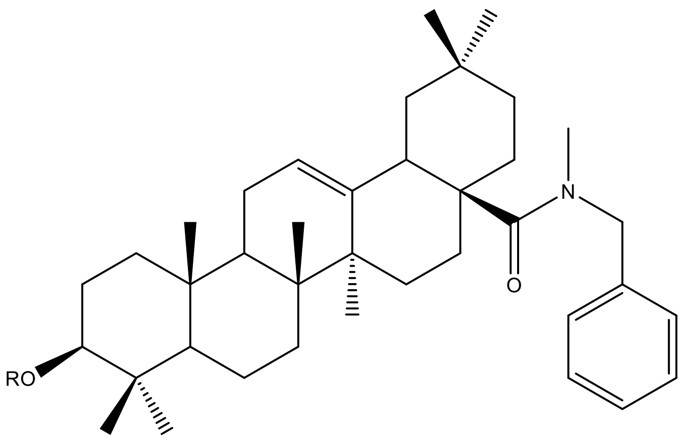
	R
5b	-β-D-Glu-(1-3)-β-D-Fuc



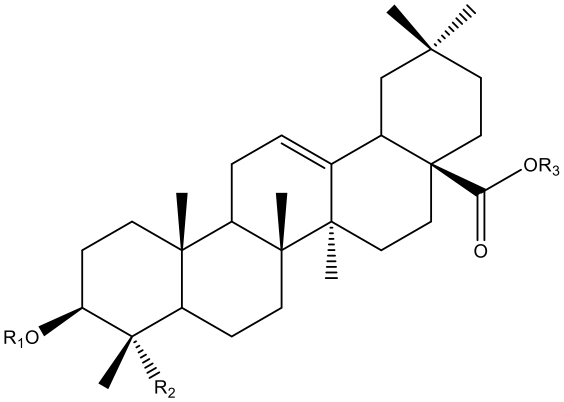
	R_1	R_2
5e	xylitol	-β-D-Glu-(1→3)-β-D-fuc
5f	xylitol	-β-D-Glu-(1→2)-β-D-Glu-(1→3)β-D-fuc



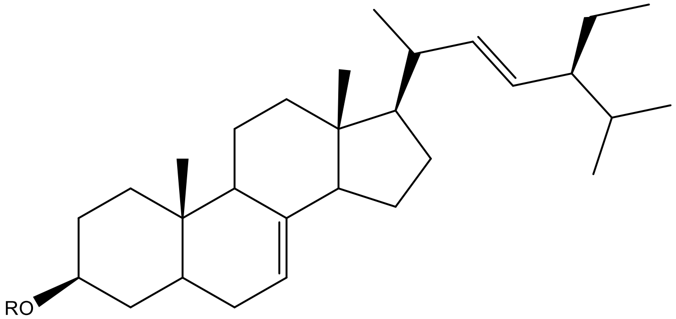
	R
6	-β-D-Glu-(1→4)-β-D-Xyl



	R
7	-α-L-Rha-(1→2)-[α-L-Rhm-(1→4)]-β-D-Glu



	R₁	**R₂**	**R₃**
8	-Glu	CH3	COOH
9	-Glu	CHO	-Glu
10	-Glu	CH3	-Glu



	R
11	-β-D-Glu

Fig.3 Chemical structures of saponins

3. Discussion

Currently no specific treatment is available for the new virus (SARS-COV-2). Thus, identification of effective drugs is urgently needed to control the spread of this disease. Several saponin-type molecules have been of interest to researchers because of their pharmacological properties, in particular antiviral properties. They could become promising agents for the treatment of COVID-19.

3.1. In vivo and in vitro

Glycyrrhizin

Glycyrrhizin is a triterpene-like saponin extracted from *Glycyrrhiza glabra* which has several biological functions. It is one of the promoting agents because it has activity against SARS-CoV in vitro [5]. Glycyrrhizin has been shown to inhibit viral adsorption and penetration, but there is also considerable evidence to show that glycyrrhizin can interact with SARS-COV replication. Glycyrrhizin inhibited the replication of two clinical isolates of SARS-associated coronavirus (FFM-1 and FFM-2) in Vero cells, by inhibiting the cytopathic effect of the virus with an EC50 of 300 mg /mL, while being non-cytotoxic to host cells. In infected Vero-E6 cells, 10 clinical isolates of the SARS coronavirus were tested by Glycyrrhizin and it was active. 200 mg of Glycyrrhizin was administered intravenously, 80 µg/mL was the value of the peak serum concentration which was insufficient to induce the desired biological effects (EC50> 400 µg/ml). In addition to increase the activity of Glycyrrhizine against SARS-CoV, we can make chemical modifications on its structure, in particular the amide derivatives and the conjugates of amino acids, but this modifications can increase the cytotoxicity [13]. Thus, the selectivity index has been minimized compared to glycyrrhizin (SI $\geq$ 65) [16]. However, it is necessary to consider the side effects of glycyrrhizin, especially in elderly patients with heart disease and hypertension. In addition, reliance only on in vitro results and animal experiments is not sufficient to judge the biological activity of Glycyrrhizin. Therefore, the clinical efficacy in humans, as well as the optimal dose and duration of treatment should be checked and evaluated in detail [5].

Escin

Escin represents a natural mixture of triterpene saponins or certain isomers of escin saponins isolated from seeds of *Aesculus hippocastanum L, Aesculus wilsonii Rehd* and others. Escin presents anti-edema activity and has been used to treat acute edema clinically. It also shows potent anti-inflammatory activities by inhibiting inflammatory cytokines such as IL-6, TNF-α and IL -1β and has antiviral activity on several viruses including SARS-CoV. In Vero E6 cells infected with SARS-CoV, escin was effective with an EC50 of 6 µM. Because of these properties, scientists have promoted the use of escin in COVID-19 pneumonia. Recently, Sodium Aescinate (injections) has been registered in clinical centers:

In China (ChiCTR2000029742) for the purpose of evaluating the efficacy and safety of sodium aescinate for injection compared to conventional therapy in patients with COVID-19 and to compare the efficacy of conventional therapy plus sodium aescinate for injection and conventional therapy plus glucocorticoids. A randomized parallel controlled trial is underway.

In Italy (NCT04322344) COVID-19 patients take escin orally (40 mg 3 times/day) or injectable (20 mg intravenously once a day) for 12 days, compared to standard therapy. Usually, a randomized double-blind parallel controlled trial is required to assess the effectiveness of treatment and must be performed to reach a scientific conclusion.

Even though the treatment of patients with COVID-19 pneumonia is urgent. Thus, future clinical trials for COVID-19 pneumonia must be intensively designed [4].

Platycodin D

Platycodin D is a triterpene saponin and the major compound of *Platycodon grandiflorum*, exhibits important antiviral properties against several viruses such as type 2 breeding pigs, respiratory syndrome virus (PRRSV) and hepatitis C virus (HCV). Recently, Platycodin D was tested against SARS-COV-2 and it was revealed that it requires both the S protein of SARS-CoV-2 and ACE2 in host cells for its virus inhibitory effect. In two cell lines: H1299 cells overexpressing ACE2 (ACE2 +) and HEK293T cells overexpressing TMPRSS2 (ACE2 / TMPRSS2 +), Platycodin D inhibited entry of SARS-CoV-2 into ACE2 + and ACE2 / TMPRSS2 + cells and IC50 values were determined at 0.69 and 0.72 respectively unlike E64d and chloroquine which were blocked entry of SARS-CoV-2 only into cells (ACE2 +) and camostat and nafamostat which were blocked entry of SARS-CoV-2 into cells (ACE2 / TMPRSS2 +) only. Mechanically, Platycodin D prevents host entry of SARS-CoV-2 by redistributing membrane cholesterol to prevent membrane fusion, which can be restablished by treatment with a PD encapsulating agent [15].

Saikosaponins

Saikosaponins are triterpene saponins isolated from *Bupleurum falcatum L* and *Radix bupleuri* known by these anti-inflammatory properties. Saikosaponin A inhibits the production of interleukins (IL-6, IL-8 and IL-10), which are responsible for the cytokine storm in COVID-19 patients. Thus, saikosaponins have antiviral properties against coronaviruses in vitro. aikosaponins A, B2, D and C were tested against HCOV-229E, saikosaponin B2 showed the best EC50 value and was blocked viral infection by inhibiting adsorption, virus penetration and replication [2], [16], [22].

Ginsenoside

Ginsenoside Rg6 is a steroidal-type saponin isolated from black ginseng, known for their biological activity, in particular anti-inflammatory activity by suppressing systemic inflammatory responses mediated by TLR-4, thanks to these properties and according to studies which have showed that disease caused by infection with SARS-COV2 virus is associated with decreased albumin level, increased NETosis, blood coagulation and cytokine level, NAB-Rg6 steroid ginsenoside nanostructures were formed in applying NAB technology then they were modified into PNAB-Rg6 by introducing a fraction of polyethylene glycol (PEG) at the albumin site in order to promote the prolonged bioactivity of steroidal ginsenoside saponins,. The use of these nanotherapeutics may reduce factors related to histone H4 and subsequent cytokine storm via downregulation of the NF-κB and SREBP2 signaling pathways in blood samples from patients with COVID-19. The validation evaluation of this experiment was carried out by animal experiments which showed efficacy of these drugs in attenuating tissue damage and cytokine storm thus promoting survival rate. For this an in-depth investigation is required on PNAB-ginsenoside to research therapeutic agents against SARS-COV 2 [17].

N- {3b-O- [2, 4-di-O-(a-L-rhamnopyranosyl) -b-Dglucopyranosyl]-olean-12-en-28-oyl}-benzylamine

Oleanolic acid is a pentacyclic triterpene of the oleanane type, there derivatives have powerful antiviral properties against various viruses such as: influenza A virus (IAV), Ebola virus (EBOV), hepatitis C virus (HCV) and other viruses by disrupting viral entry into host cells (blocking virus-host fusion by binding to viral glycoproteins). These viruses as well as COVs are enveloped viruses belong to fusion proteins (type I). Based on the results which revealed that these enveloped viruses could have the same mechanism of entry despite different cell receptors and various glycoproteins, it was speculated that oleanolic acid analogs are a potential scaffold for the discovery of potential entry inhibitors of the SARS-CoV-2 virus. 3-O-b-chacotriosyl oleanolic acid benzyl ester exhibited inhibition of SARS-CoV-2 virus entry via (S) glycoprotein binding with an IC50 value = 16.75 mM in vitro. As well as the series of these analogs whose analog named 12f showed good inhibition with an IC50 value of 0.97 mM, this inhibition was mediated by the direct interaction with the S2 subunit of the S protein of SARS- CoV-2 to block membrane fusion [1].

Esculentoside A

Esculentoside A is a triterpene saponin isolated from the roots of *Phytolacca esculenta* used for the treatment of viruses and inflammation. Esculentoside A has been tested against HCoV-OC43 coronaviruses in HCT-8 cells. The results showed that Esculentoside A could protect HCT-8 cells against infection with the virus [3].

3.2. In-silico

Esculentoside A (EsA) docked by AutoDock Vina software with S-protien (PDB ID :6LZG, 6M0J, 6VW1,7A94, 6XR8-142) gave the best binding score energy of -13,1 Kcal/mol ; The binding residues and the number of H-bonds related to the EsA-S-protein interaction were summarized in tab. 2.

Molecular docking results showed that EsA had a strong binding affinity with the spike glycoprotein from SARS-CoV-2. These results demonstrated that EsA can act as a spike protein blocker to inhibit SARS-CoV-2 [3].

The moleculaire docking of Saikosaponin A performed using AutoDock Vina v.1.0.2 software with M^{pro} (PDB ID : 6LU7, 1R4L) showed the following binding score energy -8,8 Kcal/ mol and -11 Kcal/ mol. The binding residues and the number of H-bonds related to the Saikosaponin A – M^{pro} interactions were summarized in tab. 2.

According to our docking studies, saikosaponin A , glycyrrhizin can directly bind to both host cell target ACE2 receptor and viral target main protease, indicating their potential for 2019-nCoV treatment [18].

Saikosaponin A docked by Schrodinger Maestro 2018-1 MM software with NP15(PDB ID : 6W01) and s-protien (PDB ID : 6VSB) gave the respectively binding score energy -4.725Kcal/ mol and -5,143 Kcal.

The moleculaire docking of saikosaponin -V performed using Schrodinger Maestro 2018-1 MM software with S-protiene NP15 (PDB ID : 6W01) and S-protien (PDB ID : 6VSB) showed the following binding score energy – 8,358 Kcal/ mol and – 8,299 Kcal/ mol ; The binding residues and the number of H-bonds related to the saikosaponin -V-S-protein and NP15 interactions were summarized in tab. 2.

Saikosaponin-V docked by Schrodinger Maestro 2018-1 MM software with Human interleukin-6 receptor (PDB ID :IN26) gave the binding score energy of -7,077 Kcal/ mol.

The moleculaire docking of saikosaponin-U performped using Schrödinger maestro 2018-1 MM software with NP15 (PDB ID : 6W01) and S-protien (PDB ID : 6VSB) showed the following binding score energy -8,358 Kcal/ mol and -8,429 Kcal/ mol ; The binding residues and the number of H-bonds related to the saikosaponin-U-S-protein and NP15 interactions were summarized in tab. 2.

Saikosaponin-U docked by Schrodinger Maestro 2018-1 MM software with Human interleukin-6 receptor (PDB ID : 1N26) gave the binding score energy of -6,987 Kcal/ mol.

The moleculaire docking of Saikosaponin-C performped using Schrödinger maestro 2018-1 MM software with S-protiene NP15 (PDB ID : 6W01) and S-protien (PDB ID : 6VSB) showed the following binding score energy -6,981Kcal/ mol and -7.274Kcal/ mol ; The binding residues and the number of H-bonds related to the saponine u-S-protein and NP15 interactions were summarized in tab. 2.

Saikosaponin-C docked by Schrodinger Maestro 2018-1 MM software with NADPH-Oxidase 5 (PDB ID : NOX5) gave the binding score energy of - 9.202 K cal/ mol.

Molecular docking studies revealed that IL6 in complex with Saikosaponin-U and Saikosaponin-V, NOX5 in complex with saikosaponin-C have good docking. The docking study was performed on the crystal structure of the dehydrogenase domain of NOX5. In NOX5 binding pocket, Saikosaponin-C was found to be the best fit ligand, with the docking score of - 9.202 kcal/mol [20].

The moleculaire docking of Saikosaponin-B2 performped using Schrödinger maestro 2018-1 MM software with S-protiene NP15 (PDB ID : 6W01) and S-protien (PDB ID : 6VSB) showed the binding score energy of -4,697Kcal/ mol and -6,19 Kcal/ mol .

Saikosaponin-D docked by Schrodinger Maestro 2018-1 MM software with S-protiene NP15 (PDB ID : 6W01) and S-protien (PDB ID : 6VSB) gave the following binding score energy of -3.738 Kcal/mol and -5,638 Kcal/ mol.
From the docking studies, the Saikosaponins U and V gave the best binding energy in connection with both the proteins suggesting them to be future research molecules as they mark the desire interaction with NSP15, which is responsible for replication of RNA and also with 2019-nCoV spike glycoprotein which manage the connection with ACE2 [19].

The moleculaire docking of 3-*O*-*β*-ᴅ-glucopyranosyl-spinasterol **(11)** performped using PyRx

0.9.4 virtual screenig software with M^{pro}(PDB ID : 6LU7) showed the binding score energy of –7.13 Kcal/ mol. The binding residues and the number of H-bonds related to the 3-*O*-*β*-ᴅ-glucopyranosyl-spinasterol – M^{pro} interaction were summarized in tab. 2 .

3-*O*-*β*-ᴅ-glucopyranosyl-oleanolic acid **(8)** docked by PyRx 0.9.4 virtual screenig software with M^{pro}(PDB ID : 6LU7) gave the binding score energy of –7.29 Kcal/ mol; The binding residues and the number of H-bonds related to the 3-*O*-*β*-ᴅ-glucopyranosyl-spinasterol - $M^{pro}$the interaction were summarized in tab. 2.

The moleculaire docking of lucyoside F **(9)** performped using PyRx 0.9.4 virtual screenig software with M^{pro}(PDB ID : 6LU7) showed the binding score energy of –7.47 Kcal/ mol. The binding residues and the number of H-bonds related to the lucyoside F – M^{pro} interaction were summarized in tab. 2.

lucyoside H **(10)** docked by PyRx 0.9.4 virtual screenig software with M^{pro} (PDB ID : 6LU7) gave the binding score energy –7.54 Kcal/ mol; The binding residues and the number of H-bonds related to the lucyoside H- M^{pro} the interaction were summarized in tab. 2.

From the docking results, it was found that the isolated saponins (**11, 8-10**) bind to the substrate binding pocket of SARS-CoV-2 M^{pro} with docking energy scores of -7.13, -7.29, -7.47 and -7.54 kcal /mol, respectively. Moreover, it was observed that lucyoside H (**10**), an oleanane saponin illustrated -7.54 kcal/mol binding energy thereby providing dramatic and approximate effect on the anti-SAR-CoV-2 activity along with N3 inhibitor.

The other oleanane saponin, lucyoside F (**9**) displayed a slightly lower effect on the protein than compound (**10)** and N3 inhibitor with a binding energy value of -7.47 kcal /mol. Saponins (**11)** and **(8)** showed a significant effect on the protein of SARS-CoV-2 with the binding energy of –7.13 and –7.29 kcal.mol- 1, respectively [21].

The molecular docking of glycyrrhizin with S-protein showed the binding score energy of -9 Kcal/ mol. The binding residues and the number of H-bonds related to the - N3 protease interaction were summarized in tab. 2.

glycyrrhizin docked by AutoDock Vina v.1.0.2 software with M^{pro}(PDB ID : 6LU7, 1R4L) gave the following binding score energy of -8, 9 Kcal/ mol and -9,9 Kcal/ mol; The binding residues and the number of H-bonds related to the glycyrrhizin - M^{pro} the interaction were summarized in tab. 2.

Molecular docking studies indicated that glycyrrhizin has a possible biding to human ACE2 molecules, which act as receptors for the S-protein present on the membrane of 2019-nCoV [16].

4. Conclusion

Phytoconstituents have always been of interest in therapeutic use due to their minimal side effects unlike synthetic products. Saponins are widely distributed in the plant kingdom. Given their wide range of biological activities they have used to cure a multitude of diseases such as bacterial, fungal and viral infections.With the spread of the 2019-nCoV epidemic A cumulative motivation towards the use of saponin was observed.

After our examination, we can conclude that, glycyrrhizin gave preliminary results of its potential against the new coronavirus 2019 in vitro, as well as saikosaponines. Escine has also shown clinical efficacy against Sars-CoV and clinical trials against SARS-CoV 2 are underway. From all the simulation studies on proteins, it can be concluded that Saikosaponin U and V, glycyrrhizin, Esculentoside A would be the future research interest ligand.

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