

RESEARCH ARTICLE

Molecular Docking of Phytochemical Compounds of *Momordica charantia* as Potential Inhibitors against SARS-CoV-2

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Abstract: Background: Coronavirus disease 2019 (COVID-19) has been recently declared as a global public health emergency, where the infection is caused by SARS-CoV-2. Nowadays, there is no specific treatment to cure this infection. The main protease (M^{pro}) of SARS-CoV-2 and SARS spike glycoprotein-human ACE2 complex have been recognized as suitable targets for treatment, including COVID-19 vaccines.

Objective: In our current study, we identified the potential of *Momordica charantia* as a prospective alternative and a choice in dietary food during a pandemic.

Materials and Methods: A total of 16 bioactive compounds of *Momordica charantia* were screened for activity against 6LU7 and 6CS2 with AutoDockVina.

Results: We found that momordicoside B showed the lowest binding energy compared to other compounds. In addition, kuguaglycoside A and cucurbitadienol showed better profiles for drug-like properties based on Lipinski's rule of five.

Conclusion: Our result indicates that these molecules can be further explored as promising candidates against SARS-CoV-2 or *Momordica charantia* can be used as one of the best food alternatives to be consumed during the pandemic.

Keywords: Antiviral, COVID-19, molecular docking, *Momordica charantia*, SARS-CoV-2, phytochemical compounds.

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1. INTRODUCTION

In 2020, the SARS-CoV-2 virus caused a pandemic and since then, it has become a public health emergency of international concern [1]. People have become more aware of healthy life and realized the importance of washing hands frequently, avoiding stress and crowded areas, doing regular exercise, and consuming healthy foods, such as fruits and vegetables [2]. In this emergency, it is difficult to discover novel drugs with clinical trials as it requires ample time and sources. Furthermore, the use of antiviral drugs in the event of viral infection has shown a restricted effectivity and severe adverse effect. Therefore, it is important to find natural remedies for the prevention and treatment of SARS-CoV-2.

For decades, natural products have been used for the treatment of various diseases and are well tolerated for their side effects [3]. One of the natural products beneficial for the treatment of some infectious diseases is *Momordica charantia*, edible fruit with a bitter taste that has been used traditionally as an antidiabetic and anti-infective drug.

Several antiviral activities of *Momordica charantia* have been reported. It has been known to have inhibitory activity against different subtypes of influenza A, human herpes virus-3, and hepatitis B virus [4-6].

To study the possibility of *Momordica charantia* as a prospective alternative and a choice in dietary food during this pandemic, we performed molecular docking of bioactive compounds of this plant against two important target proteins, SARS-CoV-2 main protease (M^{pro}, also known as 3C-like protease) and SARS spike glycoprotein-human ACE2 complex. M^{pro} is a key enzyme of coronaviruses and plays a critical role in mediating viral replication and transcription, making it the optimal target for SARS-CoV-2 [7]. SARS spike glycoprotein-human ACE2 complex has been considered as a suitable target in treating SARS-CoV-2 diseases. The structural spike glycoprotein of SARS-CoV-2 interacts with angiotensin-converting enzyme 2 (ACE2), allowing the virus to penetrate the human host cell [8].

Recently, molecular docking has gained much attention for effective techniques and advanced strategies related to the discovery of a novel or repurposed drug to combat the pandemic [9]. Docking assists in drug development based on the characteristic interaction between the drug molecule (ligand) and receptor [10]. Abdillah *et al.* reported that

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compounds of the *Momordica charantia* have potent inhibitory activity against main protease and papain-like protease, important enzymes of SARS-CoV-2 [11]. The novelty of this study is that it specifically focuses on the inhibitory activity of terpenoid and steroid compounds of *Momordica charantia* against M^{pro} and SARS spike glycoprotein-human ACE2 complex of SARS-CoV-2. Additionally, the drug-likeness of compounds of *Momordica charantia* is also presented in this study.

2. MATERIALS AND METHODS

2.1. Ligand Preparation

A total of 16 phytochemical compounds were found to present in *Momordica charantia*. 4 US FDA-approved drugs were retrieved from the NCBI PubChem in .sdf format. The 3D or 2D structures of ligands were prepared using Marvin Sketch software.

2.2. Protein Preparation

The protein structure of M^{pro} in complex with an inhibitor N3 and SARS spike glycoprotein-human ACE2 complex were obtained from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (<https://www.rcsb.org/>) with PDB ID: 6LU7 and 6CS2, respectively. Protein structures were optimized and cleaned by removing other heteroatoms including water using YASARA software.

2.3. Molecular Docking

Molecular docking was performed by AutoDockVina. The ligands and protein were loaded into the Auto Dock Tools program and docking calculations were simulated on the protein model. The protein-ligand interactions were visualized and analyzed using PyMOL.

3. RESULTS AND DISCUSSION

Several research works have been conducted worldwide to combat coronavirus infection. Several antiviral and antimalarial drugs have been examined for their possibility to be used against SARS-CoV-2 [12, 13]. In this study, we first selected the best COVID-19 drug candidate, an FDA-approved repurposed drug. We then examined the binding affinity of the drugs to SARS-CoV-2 M^{pro} and spike glycoprotein-human ACE2. SARS-CoV-2 M^{pro} is an important protease for the replication and maturation of SARS-CoV-2,

making it a potential target for SARS-CoV-2 infection treatment [14]. Moreover, the spike glycoprotein (S) of the SARS-CoV-2 binds angiotensin-converting enzyme 2 (ACE2), which is a human protein receptor, and facilitates fusion of the viral and human cells, thus mediating the entry of the viral spike glycoprotein into human cells [15]. Our docking data showed that remdesivir has the lowest binding energy against M^{pro} and SARS spike glycoprotein-human ACE2 complex with values of -7.5 and -8.9 kcal/mol, respectively (Table 1). Considering these results, we then investigated the bioactive compounds of *Momordica charantia* and compared their efficacy with remdesivir as a strong candidate against SARS-CoV-2.

From Table 2, we found that momordicoside A, B, C, and D have shown the lowest binding energy to M^{pro} ranging from -7.8 to -9.0 kcal/mol. On the other hand, momordicoside A, momordicoside B, 5-beta-cucurbitane, cucurbitadienol, and kuguaglycoside A showed the lowest binding affinity to SARS spike glycoprotein-human ACE2 complex in the range of -9.6 to -9.8 kcal/mol. Among them, momordicoside B was found as a potential inhibitor of these proteins. Inhibition of SARS spike glycoprotein-human ACE2 complex is important to prevent viral entry to human cells. However, some patients may contraindicate with this mechanism of treatment. Cancer patients who are sensitive to SARS-CoV-2 infection will suffer from the inhibition of ACE2 protein because it stimulates the patient's resistance to chemotherapy [16]. In order to understand the benefit and risk of SARS-CoV-2 treatment by the two-enzyme inhibition therapy, further *in vitro*, *in vivo*, and clinical studies need to be conducted.

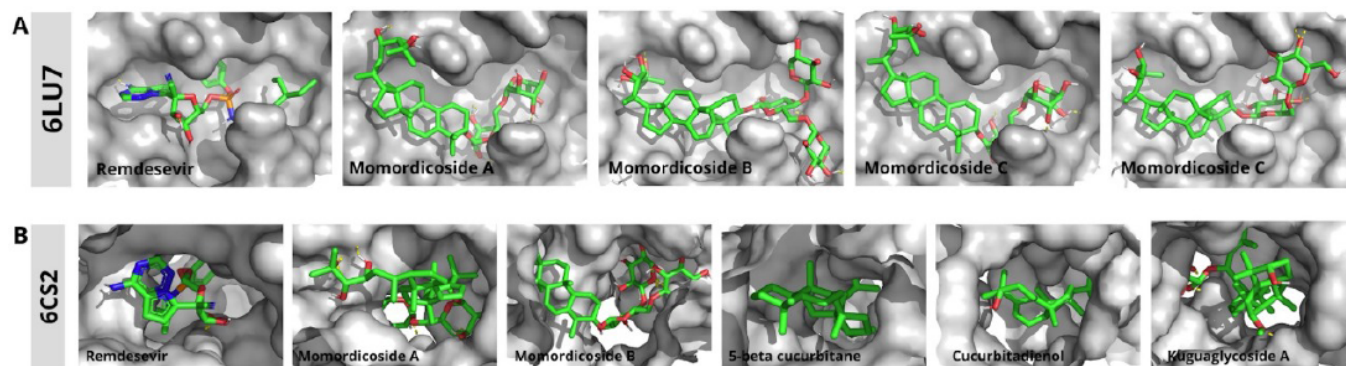
To further understand the inhibitory effect of the top-ranked bioactive compounds of *Momordica charantia*, we illustrated the docking poses and protein-ligand interactions. As we expected, our recent molecular docking data revealed that the hit compounds identified were likely to occupy the same pocket as remdesivir (Fig. 1). Momordicoside B formed hydrogen bonds with amino acid residues of M^{pro}, THR-26, H-41, ASN-119, GLY-143, THR-190, and GLN-192. There were also hydrophobic interactions formed between momordicoside B and THR-25, SER-46, MET-49, LEU-141, HIS-164, GLU-166, PRO-168, and ALA-191 (Fig. 2 and Table 3). In the SARS spike glycoprotein-human ACE2 complex, hydrogen bonds and hydrophobic interactions were found between momordicoside B and GLN-744, ASN-942, THR-988, GLN-992, ARG-996 and ALA-748, ASP-932, GLN-936, VAL-945, SER-985, TYR-989, LEU-994, respectively (Fig. 3 and Table 4).

Table 1. Binding affinity of antiviral and antimalarial drugs with COVID-19 main protease (M^{pro}) and SARS spike glycoprotein-human ACE2 complex.

Pubchem ID	Drug	Predicted ΔG_{bind} (kcal/mol)	
		6LU7	6CS2
121304016	Remdesivir	-7.5	-8.9
492405	Favipiravir	-4.9	-4.9
2719	Chloroquine	-5.9	-7.6
2165	Amodiaquine	-7.4	-8.3

Table 2. Binding affinity of phytochemical compounds of *Momordica charantia* with COVID-19 main protease (M^{pro}) and SARS spike glycoprotein-human ACE2 complex.

PubChem ID	Compounds	Predicted ΔG_{bind} (kcal/mol)	
		6LU7	6CS2
71306378	5-alpha cucurbitane	-6.8	-9.5
71306377	5-beta cucurbitane	-7.1	-9.8
14543446	Cucurbitadienol	-6.6	-9.7
57402436	Kuguaglycoside A	-7.2	-9.6
101447827	Kuguaglycoside C	-6.9	-7.8
101862286	Kuguaglycoside E	-7.0	-9.4
56961673	Kuguaglycoside G	-7.2	-8.0
102066427	Momordicilin	-7.5	-9.5
14807332	Momordicin I	-7.2	-9.1
101019708	Momordicin II	-7.2	-9.3
71717038	Momordicoside A	-7.8	-9.6
131751677	Momordicoside B	-9.0	-9.8
71717037	Momordicoside C	-7.8	-9.5
131751649	Momordicoside D	-7.8	-7.6
71717036	Momordicoside I	-7.2	-7.1
131751990	Momordicoside K	-6.8	-6.8

**Fig. (1).** Binding mode in protein pocket. (A) The docking results of remdesivir and four top-ranked bioactive compounds with Mpro (6LU7, shown as grey background) and inhibitors are shown in the green stick. (B) The docking results of remdesivir and five top-ranked bioactive compounds with SARS spike glycoprotein-human ACE2 complex (6CS2, shown as grey background) and inhibitors are represented by a green stick. (A higher resolution / colour version of this figure is available in the electronic copy of the article).**Table 3.** Protein-ligand interactions of top-ranked bioactive compounds of *Momordica charantia* screened against SARS-CoV-2 M^{pro} receptor binding site.

No	Ligand	ΔG_{bind} (kcal/mol)	Protein-ligand Interactions	
			Hydrogen Bond	Hydrophobic Interactions
1	Remdesivir	-7.5	THR-26, SER-46, GLY-143, HIS-163, GLU-166	THR-25, MET-49, LEU-141, PRO-168, HIS-172, ALA-191, GLN-192
2	Momordicoside A	-7.8	GLY-143, SER-144, CYS-145, HIS-163, HIS-164	THR-25, THR-26, TYR-118, HIS-41, LEU-50, GLU-166, ALA-191, GLN-192,
3	Momordicoside B	-9.0	THR-26, H-41, ASN-119, GLY-143, THR-190, GLN-192	THR-25, SER-46, MET-49, LEU-141, HIS-164, GLU-166, PRO-168, ALA-191
4	Momordicoside C	-7.8	THR-26, LEU-141, GLY-143, SER-144, CYS-145, HIS-163, HIS-164, GLN-189	THR-25, GLU-47, MET-49, LEU-50, ASN-142, GLU-166, PRO-168, ALA-191
5	Momordicoside D	-7.8	THR-24, THR-26, LEU-141, ASN-142, GLY-143, SER-144, CYS-145	THR-25, HIS-41, MET-49, TYR-118, GLU-166, PRO-168, THR-190

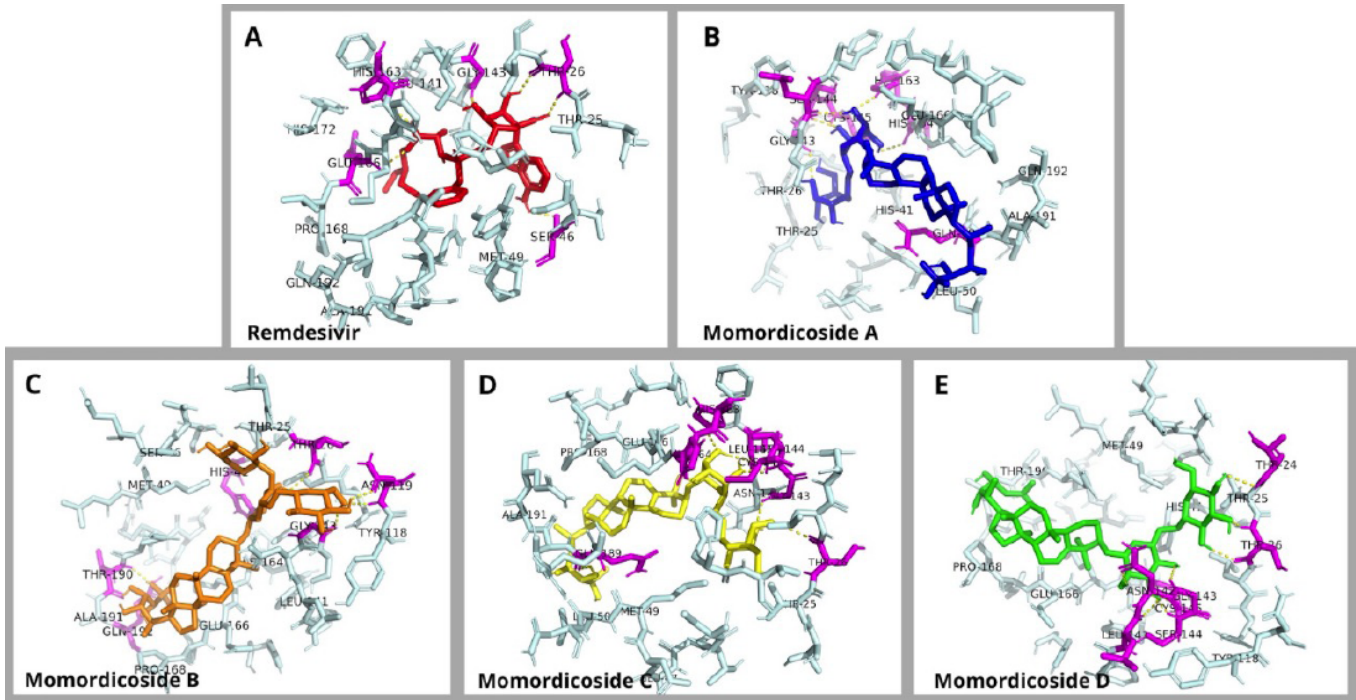


Fig. (2). *Momordica charantia* leads to phytochemical interaction with Mpro. The hydrogen bonds are indicated by the yellow dashed lines with amino acid residues (magenta stick). The hydrophobic interactions are represented by the pale cyan stick. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

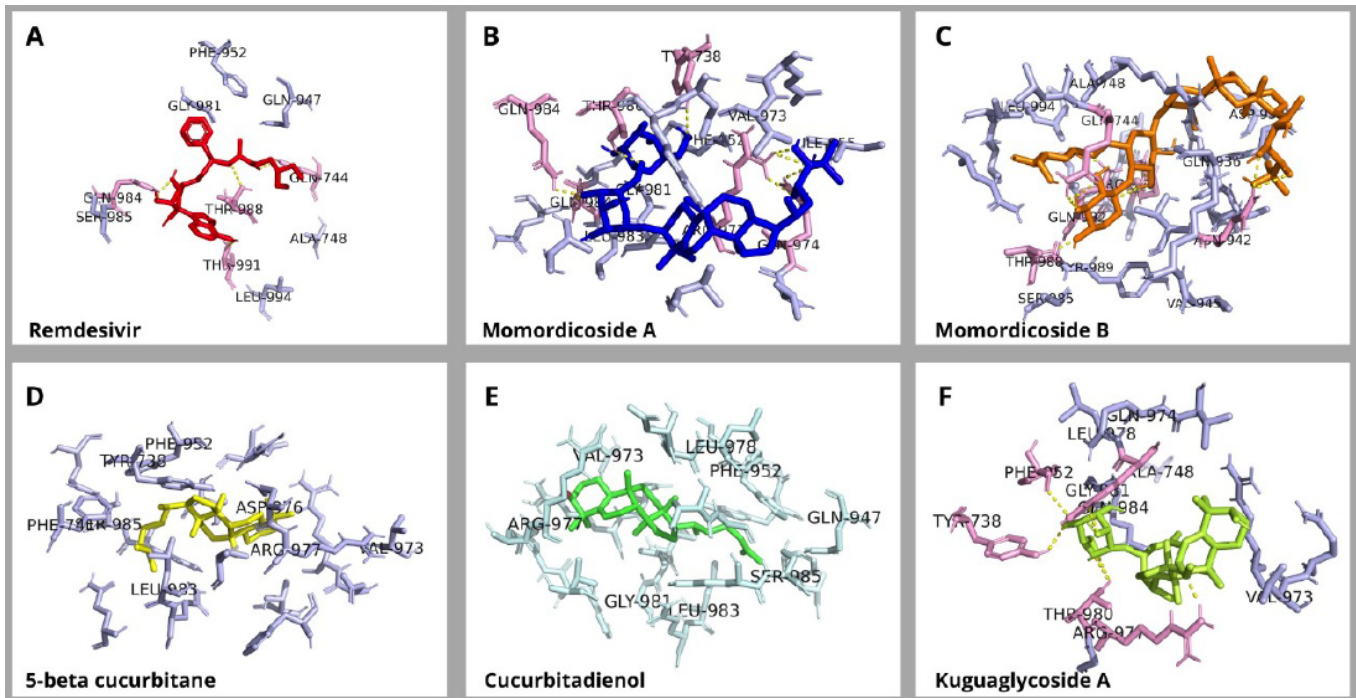


Fig. (3). *Momordica charantia* leads to phytochemical interaction with SARS spike glycoprotein-human. The hydrogen bonds are indicated by the yellow dashed lines with amino acid residues (pink stick). The hydrophobic interactions are represented by the light blue stick. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Table 4. Protein-ligand interactions of top-ranked bioactive compounds of *Momordica charantia* screened against SARS spike glycoprotein-human ACE2 complex.

No	Ligand	ΔG_{bind} (kcal/mol)	Protein-ligand interactions	
			Hydrogen Bond	Hydrophobic Interactions
1	Remdesivir	-8.9	GLN-744, GLN-984, THR-988, THR-991,	ALA-748, GLN-947, PHE-952, GLY-981, SER-985, LEU-994
2	Momordicoside A	-9.6	TYR-738, GLN-974, ARG-977, THR-980, GLN-984	PHE-952, GLU-972, VAL-973, GLY-981, LEU-983
3	Momordicoside B	-9.8	GLN-744, ASN-942, THR-988, GLN-992, ARG-996	ALA-748, ASP-932, GLN-936, VAL-945, SER-985, TYR-989, LEU-994
4	5-beta-cucurbitane	-9.8	No hydrogen bonds	PHE-741, TYR-738, PHE-952, VAL-973, ASP-976, ARG-977, LEU-983, SER-985
5	Cucurbitadienol	-9.7	No hydrogen bonds	GLN-947, PHE-952, VAL-973, LEU-978, GLY-981, LEU-983, SER-985
6	Kuguaglycoside A	-9.6	TYR-738, PHE-952, ARG-977, THR-980	ALA-748, VAL-973, GLN-974, LEU-978, GLY-981, GLN-984

Table 5. Drug Likeness.

No	Ligand	MW <500	cLogP <5	HBA <10	HBD <5	TPSA ≤140
1	Remdesivir	602.6	1.9	13	4	204
2	Momordicoside A	817	1	15	11	259
3	Momordicoside B	949.1	-0.5	19	13	318
4	Momordicoside C	801	2	14	10	239
5	Momordicoside D	783	3.2	13	9	219
6	5beta-cucurbitane	414.7	12.1	0	0	0
7	Cucurbitadienol	426.7	9.2	1	1	20.2
8	Kuguaglycoside A	634.9	5.7	8	5	129

MW: molecular weight, HBA: hydrogen bond acceptor, HBD: hydrogen bond donor, TPSA: topological polar surface area.

Table 6. Bioactive compounds of *Momordica charantia* whole plant.

Bioactive Compound	Distribution	Function	References
Heteropolysaccharides	Various parts of plants	Immunomodulator, antidiabetic, antitumor, antimicrobial, α -amylase inhibition	[18-20]
Proteins and peptides	Fruit, flesh, leave, seed	Antimicrobial, antitumor	[21, 22]
Saponins	Fruit, flesh, seed, root	Antidiabetic, antihyperglycemic, antiviral	[23]
Terpenoids	Fruit, stem, leave, seed	Anticancer, antidiabetic, antioxidant	[24-28]
Flavonoids and phenolics	Fruit, leave, stem, flower, root	Antioxidant, anti-inflammatory	[29-31]
Sterols	Pericarp, fruit	Antimicrobial	[32]

Lipinski's rule of five was used to confirm the drug-likeness of our top-ranked compounds. According to Table 5, the compounds of *Momordica charantia* and remdesivir did not meet all the criteria of Lipinski's rule of five. The lipophilicity profile of momordicoside A, B, C, and D was less than 5. However, the number of protons from donor and

acceptor of their functional group and also their molecular weight did not qualify for the rule of five. Among the hit compounds, kuguaglycoside A and cucurbitadienol revealed a better profile. Besides, these compounds were found to be within the reference range considering their topological polar surface area. Moreover, the rule of five actually did not

encompass all the natural compounds which have been marketed as drugs [17].

All the top-ranked bioactive compounds evaluated in this study belong to saponin and terpenoid groups. As shown in Table 6, saponin and terpenoids are major bioactive compounds of *Momordica charantia* and have been demonstrated as antiviral agents. Accordingly, this fruit can be suggested as one of the best food alternatives to be consumed during the SARS-CoV-2 infection pandemic. However, further investigations need to be done for better understanding and verification of *in vitro*, *in vivo*, and clinical evidence of those compounds to be used as antivirals against coronavirus.

CONCLUSION

In conclusion, several bioactive compounds of *Momordica charantia* were found to have a potential activity to inhibit the SARS-CoV-2 due to their better affinity to bind the virus proteins than the antiviral drug, namely remdesivir. Along with that, physicochemical properties of the tested saponin and terpenoid from *Momordica charantia* revealed their feasibility to be developed as the lead compounds with antiviral properties against SARS-CoV-2 infection.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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