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An *in-silico* approach to essential oil phytochemicals of *Curcuma amada* Roxb. as potential inhibitor of Covid 19 protease

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Abstract
COVID 19 pandemic caused by SARS-CoV-2, has infected millions across the globe and is still holding the grip. The Scientific world is fast experimenting to find a much more effective vaccine or drug against the elusive virus. The plant derived drugs are always preferred because of their relatively low side effects and numerous other advantages. Phytochemicals present in the essential oil of *Curcuma amada* have potential for the development of prophylactics or therapeutics against COVID-19. Essential oil-based phytomedicines include of *C. amanda*: α-Farnesene, cis-β-Farnesene, Alloaromadendrene, Alpha-Curcumene, Alpha-Pinene, Camphene and others. In this study, drug-likeness properties and ADME of all the phytochemicals in *Curcuma amada* are determined, docked with selected the COVID 19 protease and compared it with hydrochloroquinine as well as chloroquinine phosphate through *in silico* approach. The study revealed that these molecules can bind with high affinity to the virus proteases like 5R7Y, 5R7Z, 5R80, 5R81 and 5R82. It is determined that they are more or less similar to commercially available drugs like hydroxychloroquinine and chloroquinine phosphate. Furthermore, these molecules satisfy Lipenski rule of five, and ADME which indicates the potential of these phytochemicals as candidates for further research as developing drug against COVID19. These phytochemicals can be explored more for its bioactivities.

Keywords: hydroxychloroquinine, chloroquinine phosphate, 5R7Y, 5R7Z, 5R80, 5R81 5R82, zingiberaceae, lipinski rule of five, ADME

Introduction

A viral pneumonia which kept whole world static through its epidemic nature named as Covid 19 even after more than a year is still infectious (Wu *et al*., 2020) [19]. This virus affect human respiratory system adversely and it is sequence wise similar to SARS-CoV (Severe Acute Repiratory Syndrome Coronavirus) (82% identity) and the MERS-CoV (Middle East Respiratory Syndrome Coronavirus) (50% identity) (Andersen, Rambaut, Lipkin, Holmes, & Garry, 2020) [1]. It is an enveloped non-segmented positive sense RNA viruses from the family Coronaviridae and the order Nidovirales (Wu *et al*., 2020) [19]. High infectious nature of the Covid-19 virus is due to the mutation in surface glycoprotein of the virus also known as spike protein (Andersen *et al*., 2020) [1]. Acute Respiratory Distress Syndrome (ARDS) and gradual multiple organ dysfunctions are the complicated impact of infection (Zhang *et al*., 2020) [21]. Cough and fatigue, fever, headache, sputum production, dyspnoea, haemoptysis, diarrhoea and lymphopenia are the common symptoms (Rothan & Byrareddy, 2020) [16]. Rapid transmission among human makes it highly dangerous (Wang, Wang, Ye, & Liu, 2020) [19]. Covid19 has been declared as a pandemic by WHO for which the global scientific community is actively researching to develop an ultimate drug.

Curcuma amada Roxb. is a unique spice having morphological resemblance with ginger *(Zingiber officinale)* but imparts a raw mango *(Mangifera indica)* flavor (Policegoudra, Aradhya, & Singh, 2011) [14]. Thus, commonly known as mango ginger. Indo-Malayan region is the origin of *C. amada* and is distributed widely in the tropics from Asia, Africa and Australia (George & John Britto, 2016) [6]. The rhizome of *C. amada* possess numerous properties including antioxidant, antibacterial, antifungal, anti-inflammatory, platelet aggregation inhibitory, cytotoxicity, antiallergic, biopesticidal, hypotriglyceridemic, brine-shrimp lethal, CNS depressant and analgesic, enterokinase inhibitory and antitubercular activities (Policegoudra *et al*., 2011) [14]. Here, we are enduring an attempt to convincingly provide in-silico evidences for the potential of *C. amada* phytochemicals in being considered as candidates in drug development against Covid-19.

Materials and Methods

Crystal proteins structure of COVID-19 main protease (PDB IDs: 5R7Y, 5R7Z. 5R80, 5R81, 5R82) were selected and obtained from Protein Data Bank (http:// www.rscb.org) with good resolutions. They have resolution < 2Å, R-Value Free < 0.30, R-Value Work < 0.25 obtained through X-ray diffraction method. This crude structure was polished by removal of water and addition of polar hydrogen bonds. Quality of the generated model was assessed using the "Verify Protein (Profiles-3D)", a protocol of the Discovery Studio (DS). Energy minimization of the protein structure was performed by applying the "prepare protein" protocol of the DS. The dimensions of the grid box were taken in such a way that the whole protein could be considered for searching the best binding site and finally the protein structure was ready for docking. Active site of these

proteins was predicted using "Define and Edit Binding Site" protocol of Discovery studio. The obtained binding site for proteins are listed in Table 1.

Ligand preparation

A total of 17 phytocompounds from essential oil of *C.amada* were studied (George & John Britto, 2016) [6]. The 3D structure of 17 compounds were downloaded from NCBI Pubchem database ("PubChem," n.d.). All the compounds were then imported to DS and 'prepare ligands protocol' was utilized in order to add missing hydrogen bonds. The physiochemical properties of phytochemicals were taken into consideration. The prepared ligands were further filtered by applying Lipinski's properties such as molecular weight, XLog P, number of hydrogen bond donors and acceptors (Lipinski, Lombardo, Dominy, & Feeney, 1997) [12].

Prediction of ADME and molecular docking

Phytochemical properties such as absorption, distribution, metabolism and excretion (ADME) profiling of compounds were determined using the swissadme website (http://wwwswissadme.ch) (Barthe, Woodley, & Houin, 1999) [2]. Molecular docking was done in Auto dock Vina software and was visualized via Pymol software and Discovery Studio.

Results and Discussion

The Molecular weight (MW), XLogP, H-bond donors, and H-bond acceptors value of all the phytochemicals were calculated and found to be within acceptable range according to Lipinski's rule (Kortemme, Morozov, & Baker, 2003) [10]. Phytochemicals present in essential oils propitiate in Lipinski rule. Table 2 shows the lipinski rule of phytochemicals.

Various parameters like physiochemical parameters, liphophilicity and water solubility, pharmacokinetics as well as medicinal chemistry are analysed in table 3,4,5 and 6 respectively. The physiochemical parameters like molecular weight (MW), Heavy atoms, Aromatic heavy atoms, Rotatable bonds, H-bond acceptors, H-bond donor, MR (Molar refractivity), TPSA (Topological molar surface area) are depicted.

The docking scores of the essential oil phytochemicals of *curcuma amada* against five COVID19 proteases namely 5R7Y, 5R7Z, 5R80, 5R81 and 5R82 and was compared with antiviral drugs hydrooxychloroquinine and chloroquinine phosphate are depicted in Table 7.

Lipinski's rule of five and ADME

The drug likeness scores of the selected ligands were analysed to determines whether a particular molecule is similar to known drugs (Lipinski *et al*., 1997) and found to be within acceptable range according to Lipinski's rule (Kortemme, Morozov, & Baker, 2003) [10]. It is an important parameter to determine four simple physicochemical parameter ranges (MW ≤ 500, log P ≤5, H-bond donors≤ 5, H-bond acceptors ≤ 10) (Madeswaran *et al*., 2012).

To improve the quality control of drugs, we predicted the absorption, distribution, metabolism and excretion (ADME) of phytochemicals and its impurities via *in silico* methods. It helps to fasten the discovery of a drug (Kortemme *et al*., 2003) [10]. Phytochemicals present in *C.amada* considerably satisfy the ADME ranges and thus can be developed as a drug.

The interaction between the proteins and the ligands are shown in the table 8. The common bonds shown by the proteins include the van der waals, alkyl, pi alkyl, pi – sigma and conventional hydrogen bond. The special bonds include pi-sulphur bonds, unfavourable Donor – donor bond, pi-pi stacked bond and pi- pi T shaped bond.

Docking

The best docking score of phytochemicals in the *C. amada* essential oil is resulted in Alloaromadendrene against the COVID 19 proteases 5R7Y, 5R7Z, 5R80, 5R81 and 5R82 and also showed highest score against 5R7Z in comparison with the drugs hydroxychloroquinine and chloroquinine phosphate. Allomamaderene showed same docking score value with the drug chloroquinine phosphate against 5R80 protease (-5.9) and hydroxycholoroquinine against 5R82(-5.4). The interaction with 5R7z with Alloaromadendrene is depicted in the figures 1, 2 and 3. The parameter of molecular docking is binding energy which deals with the interaction between the receptor and ligand. The greater the binding energy, weaker the interaction and vice versa. Thus during any docking study, we intend to look for the ligand which displays the least binding energy, thus the best affinity among the test molecules. The study by Gao *et al*., (Gao, Tian, & Yang, 2020) [5] suggests that choloquinine phosphate can be used as a drug against COVID 19 and a slight variation was also observed in the binding energy of alloammandrene with respect to the hrdroxychloroquinine which reveals the potentiality of Alloaromadendrene to be used as a drug. Caryophyllene followed by Alloaromadendrene resulted in the next good binding energy scores. α-Farnesene and alpha curcumene also showed significantly high docking score aganist the selected protease.

Plant derived secondary metabolites may be explored as potential inhibitors against COVID-19, considering their natural occurrence, less cost of production and minimum or negligible side effects (Gao *et al*., 2020) [5]. These characteristics enable it to be used as a user-friendly drug. These phytochemicals can be modified accordingly to design new potential drug Kortemme *et al*. (Kortemme *et al*., 2003) [10] demonstrated that minimum the binding energy ion docking result, greater is the binding affinity between the ligand and the protein. Another study (Jin *et al*., 2014) [9] says that the hydrogen bond interaction determines the strength of binding between the ligand and protien high integration suggests strong binding. The active functional group of phytochemicals are completely surrounded by the binding pocket of the 5R7Y of COVID 19. Hence, they fit properly into its active site via hydrogen bonding interactions (Jin *et al*., 2014) [9]. From the results of docking analysis, it was found that all phytochemicals have antiviral inhibitory activity against 5R7Y enzyme. Traditional medicinal plants have also been used for treating diverse viral diseases for centuries. A number of natural phytochemicals experimentally proved that they have an antiviral activity against various kinds of viruses (Thirumal Kumar & George Priya Doss, 2016) [17]. Natural products and their derivatives are used in folk medicine to treat numerous ailments including viral infections (Guan *et al*., 2020) [8]. Nature provides a vast library of chemicals to explore and develop drugs for treatment of various ailments including viral diseases (Denaro *et al*., 2020) [4]. To date, a good number of herbal medicines or their constituents have

shown potential antiviral activity (Lin, Hsu, & Lin, 2014) [11]. Some early reports on the activity against CoV include concanavalin A, a phytagglutinin found in jack beans (*Canavaliaensiformis*). ConA was responsible for the transient inactivity of hemagglutinating encephalomyelitis CoV, by binding with glycosylated membrane proteins which help virus in host cell recognition (Greig & Bouillant, 1977). Tannic acid, 3-isotheaflavin-3-gallate, and theaflavin-3, 3′-digallate, three phenolic compounds from black tea exerted inhibitory effects on SARS-CoV $3CL^{pro}$ with IC_{50} values of 3, 7, and 9.5 μM, respectively (Chen *et al*., 2005) [3]. Tylophorine and 7-methoxycryptopleurine, two alkaloids isolated from *Tylophora indica* inhibited N and S protein activity as well as viral replication of enteropathogenic coronavirus transmissible gastroenteritis virus (Yang *et al*., 2010) [20].

Tables and Figures

Table 1: The best Binding site of proteins selected to dock with ligands

Proteins	X	Y	Z
5R7y	9.611	-0.428	22.905
5R7z	9.486	0.413	21.594
5R80	10.66	-3.74	22.571
5R81	12.466	1.235	22.43
5R82	9.452	0.042	21.456

Table 2: Values of Lipinski's rule of phytochemicals of *Curcuma amada* essential oil.

Compound name	Mass	Hydrogen bond donor	Hydrogen bond acceptors	LOGP	Molar refractivity
α-Farnesene	204	0	0	4.270899	64.512985
cis-β-Farnesene	204	0	0	5.201500	70.992981
Alloaromadendrene	204	0	0	5.201500	70.992981
2-Pyridinamine, 4,6-dimethyl-	122	2	2	1.280640	38.123394
Alpha curcumene	202	0	0	4.844920	68.258987
Caryophyllene	204	0	0	4.725199	66.742981
1,3,6-Octatriene, 3,7-dimethyl-, (Z)	136	0	0	3.474999	48.001987
alpha-Pinene	136	0	0	2.998699	43.751987
Bicyclo[3.1.1]heptane,6,6-dimethyl-2-methylene-, (1S)-	136	0	0	2.998699	43.751987
D-Limonene	136	0	0	3.308899	45.911987
beta.-Myrcene	136	0	0	3.474999	48.001987
Camphene	136	0	.0	2.998699	43.751991
Hydroxychloroquinine	335.5	2	4	3.011079	95.340469
Chloroquinine Phosphate	319.5	1	3	4.038679	93.928673

Table 3: Physiochemical properties analysis of phytochemicals

Molecule	Formula	MW	Heavy atoms	Aromatic heavy atoms	Rotatable bonds	H-bond acceptors	H-bond donors	MR	TPSA
α-Farnesene	$C_{15}H_{24}$	204.35	15	0	6	0	0	72.32	0
cis-β-Farnesene	$C_{15}H_{24}$	204.35	15	0	7	0	0	72.32	0
Alloaromadendrene	$C_{15}H_{24}$	204.35	15	0	0	0	0	67.14	0
2-Pyridinamine, 4,6-dimethyl	$C_7H_{10}N_2$	122.17	9	6	0	1	1	38.57	38.91
Alpha curcumene	$C_{15}H_{22}$	202.34	15	6	4	0	0	69.55	0
Caryophyllene	$C_{15}H_{24}$	204.35	15	0	0	0	0	68.78	0
1,3,6-Octatriene, 3,7-dimethyl-, (Z)	$C_{10}H_{16}$	136.23	10	0	3	0	0	48.76	0
alpha-Pinene	$C_{10}H_{16}$	136.23	10	0	0	0	0	45.22	0
Bicyclo[3.1.1]heptane, 6,6-dimethyl-2-methylene-, (1S)-	$C_{10}H_{16}$	136.23	10	0	0	0	0	45.22	0
D-Limonene	$C_{10}H_{16}$	136.23	10	0	1	0	0	47.12	0
beta.-Myrcene	$C_{10}H_{16}$	136.23	10	0	4	0	0	48.76	0
Camphene	$C_{10}H_{16}$	136.23	10	0	0	0	0	45.22	0

Table 4: Lipophilicity and water solubility parameters of phytochemicals

Molecule	Consensus Log P	Silicos-IT class	ESOL Class	Ali Class
α-Farnesene	4.96	Soluble	Moderately soluble	Moderately soluble
cis-β-Farnesene	4.97	Soluble	Moderately soluble	Moderately soluble
Alloaromadendrene	4.34	Soluble	Moderately soluble	Moderately soluble
2-Pyridinamine, 4,6-dimethyl	1.38	Soluble	Very soluble	Very soluble
Alpha curcumene	4.86	Moderately soluble	Moderately soluble	Moderately soluble
Caryophyllene	4.24	Soluble	Soluble	Moderately soluble
1,3,6-Octatriene, 3,7-dimethyl-, (Z)	3.4	Soluble	Soluble	Soluble
Alpha-Pinene	3.44	Soluble	Soluble	Moderately soluble
Bicyclo[3.1.1]heptane, 6,6-dimethyl-2-methylene-, (1S)-	3.42	Soluble	Soluble	Soluble
D-Limonene	3.37	Soluble	Soluble	Moderately soluble
beta.-Myrcene	3.43	Soluble	Soluble	Soluble
Camphene	3.43	Soluble	Soluble	Soluble

Table 5: Pharmacokinetics parameters of phytochemicals

Molecule	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	BBB permeant	GI absorption	log Kp (cm/s)
α-Farnesene	No	Yes	No	Yes	No	No	No	Low	-3.2
cis-β-Farnesene	No	Yes	No	Yes	No	No	No	Low	-3.27
Alloaromadendrene	No	Yes	Yes	Yes	No	No	Yes	Low	-4.2
2-Pyridinamine, 4,6-dimethyl	No	No	No	No	No	No	Yes	High	-6.14
Alpha curcumene	No	No	No	No	Yes	No	No	Low	-3.71
Caryophyllene	No	No	Yes	Yes	No	No	No	Low	-4.44
1,3,6-Octatriene, 3,7-dimethyl-, (Z)	No	No	No	No	No	No	Yes	Low	-4.11
alpha-Pinene	No	No	No	Yes	No	No	Yes	Low	-3.95
Bicyclo[3.1.1]heptane, 6,6-dimethyl-2-methylene-, (1S)-	No	No	No	Yes	No	No	Yes	Low	-4.18
D-Limonene	No	No	No	Yes	No	No	Yes	Low	-3.89
beta.-Myrcene	No	No	No	No	No	No	Yes	Low	-4.17
Camphene	No	No	No	Yes	No	No	Yes	Low	-4.13

Table 6: Medicinal chemistry parameters of phytochemicals

Molecule	Bioavailability Score	PAINS #alerts	Synthetic Accessibility	Brenk #alerts
α-Farnesene	0.55	0	3.72	2
cis-β-Farnesene	0.55	0	3.42	2
Alloaromadendrene	0.55	0	3.7	1
2-Pyridinamine, 4,6-dimethyl	0.55	0	1.4	0
Alpha curcumene	0.55	0	2.31	1
Caryophyllene	0.55	0	4.51	1
1,3,6-Octatriene, 3,7-dimethyl-, (Z)	0.55	0	3.63	2
alpha-Pinene	0.55	0	4.44	1
Bicyclo[3.1.1]heptane, 6,6-dimethyl-2-methylene-, (1S)-	0.55	0	3.73	1
D-Limonene	0.55	0	3.46	1
beta.-Myrcene	0.55	0	2.85	2
Camphene	0.55	0	3.5	1

Table 7: Docking score or binding energy (kcal/mol) of phytochemicals against the proteins

Phytochemicals	5R7Y	5R7Z	5R80	5R81	5R82
α-Farnesene	-4.2	-5.2	-5.3	-5.3	-4.4
cis-β-Farnesene	-4.1	-4.7	-4.9	-4.8	-4.1
Alloaromadendrene	**-5.3**	**-5.8**	**-5.9**	**-6.0**	**-5.4**
2-Pyridinamine, 4,6-dimethyl-	-4.0	-4.2	-4.8	-4.4	-4.2
Alpha curcumene	-4.5	-5.3	-5.2	-5.4	-4.6
Caryophyllene	-5.2	-5.3	-5.7	-5.2	-5.2
1,3,6-Octatriene, 3,7-dimethyl-, (Z)	-3.5	-4.3	-4.8	-4.4	-3.9
alpha-Pinene	-4.2	-4.4	-5.0	-4.2	-4.0
Bicyclo[3.1.1]heptane, 6,6-dimethyl-2-methylene-, (1S)-	-4.2	-4.3	-5.3	-4.4	-4.1
D-Limonene	-4.0	-4.6	-4.8	-4.7	-4.1
beta.-Myrcene	-3.2	-4.2	-4.6	-4.4	-3.6
Camphene	-3.8	-4.4	-4.5	-4.5	-3.9
hydroxychloroquinine	-5.5	-5.7	-6.2	-6.1	-5.4
Chloroquinine phosphate	-5.4	-5.7	-5.9	-6.1	-4.8

Table 8: Bonds involved in the interaction of protein with ligand

Common bonds with the ligands and proteins	5R7Y	5R7Z	5R80	5R81	5R82
Van der waals	+	+	+	+	+
Alkyl	+	+	+	+	+
Pi-alkyl	+	+	+	+	+
Pi- sigma	+	+	+	+	+
Pi -sulphur	+	+	_	+	+
Conventional hydrogen bond	+	+	+	+	+
Unfavourable Donor- Donor bond	+	-	-	+	-
Pi- pi stacked	-	-	+	-	-
Pi- pi T shaped	-	-	-	-	+

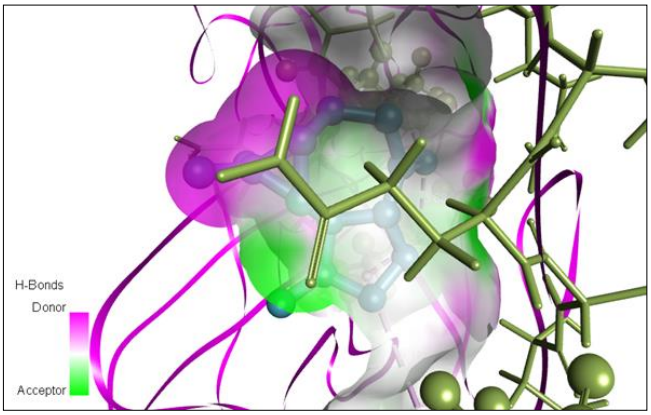

Fig 1: 5R7z interact with alloamanderene

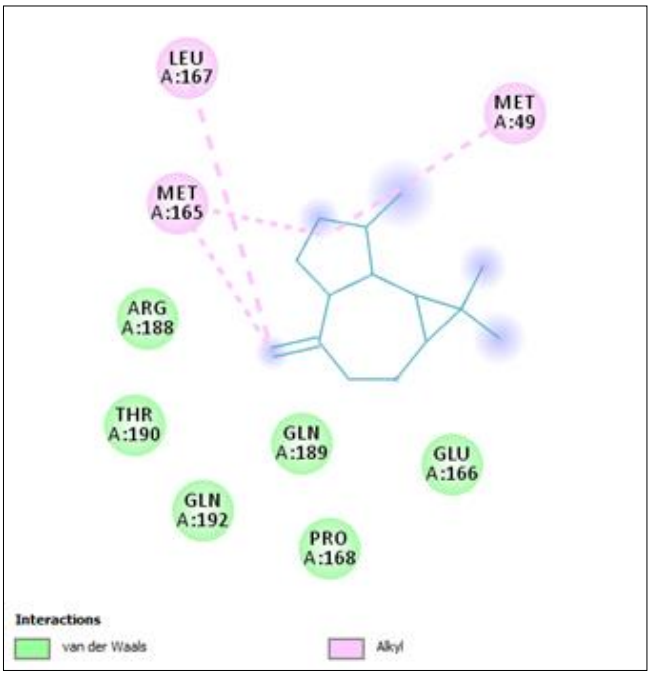

Fig 2: 2-D diagram showing the interaction between 5R7z and alloaromadendrene

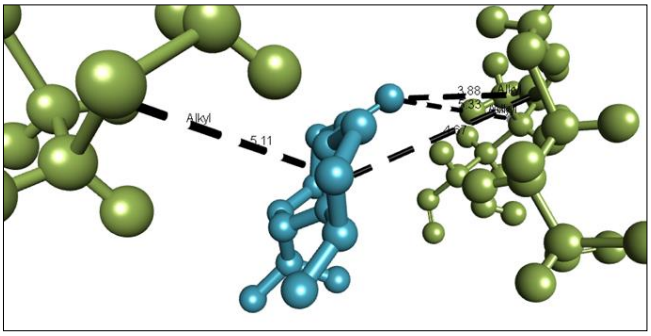

Fig 3: the bond length of the interaction between 5R7z and Alloaromadendrene

Conclusion

The world always looks forward to a drug from natural compounds due to its advantages. Recently, the world is facing a pandemic due to the Coronavirus COVID-19 which spreads all over very quickly. It is an emergency situation to find out a vaccine or drug to control it. Essential oil of *C.amada contains* phytochemicals with properties such as antiviral, antibacterial and antifungal activity. The phytochemicals were subjected to virtual screening against five proteins of covid19. 12 compounds were selected from each target which had better and significantly low binding energy as compared to the reference molecules. Based on the binding energy score, we suggest that these compounds can be tested against Coronavirus and used to develop effective antiviral drugs.

List of abbreviations

SARS-CoV- Severe Acute Respiratory Syndrome Coronavirus
MERS-CoV- Middle East Respiratory Syndrome Coronavirus
RNA- Ribonucleic acid
ARDS- Acute Respiratory Distress Syndrome
WHO- World Health Organization
DS- Discovery Studio
NCBI- National Center For Biotechnology Information
ADME - Absorption, Distribution, Metabolism and Excretion
MW- Molecular Weight
MR- Molar Refractivity
TPSA- Topological Molar Surface Area
CoV- Corona Virus

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