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آنزیم‌های مصنوعی که از داروهای گیاهی تقلید می‌کنند: رویکردی نوین در درمان کرونا

Artificial Enzymes That Imitate Herbal Medicine: A Novel Approach in COVID-19 Remedy

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چکیده

همه‌گیری COVID-19 به یک وضعیت اضطراری جدی تبدیل شده است و در حال حاضر یک نگرانی جهانی برای انسان‌ها در سراسر جهان می‌باشد. عدم مدیریت و کنترل به موقع این بیماری می‌تواند منجر به یک فاجعه‌ی انسانی گردد. بر این اساس، مداخلات درمانی مختلفی برای درمان COVID-19 در سراسر جهان انجام می‌گیرد. استفاده از داروهای گیاهی یکی از گزینه های درمانی پیشنهادی در چین و بسیاری از کشورهای دیگر است. همولوژی بالای ژنوم این ویروس با SARS و وجود شواهد قطعی از کاربردهای گیاهی در درمان و پیشگیری از SARS امیدوارکننده می‌باشد. این مقاله بر روی استفاده از داروهای گیاهی با کاربرد بالقوه برای درمان COVID-19 و ارزیابی اثرات بازدارنده این ترکیبات بر پروتئین‌های حیاتی کروناویروس با شبیه‌سازی داکینگ مولکولی تمرکز دارد. همچنین فرصتی برای آشکار کردن کاربرد آنزیم‌های مصنوعی برای درمان COVID-19 فراهم می شود. استفاده از آنزیم های مصنوعی برای درمان COVID-19 برای اولین بار در این مطالعه پیشنهاد شده است. نتایج شبیه‌سازی اتصال مولکولی نشان داد که Glycyrrhetinic acid اثر مهاری چشمگیری بر روی همه پروتئین‌های مورد مطالعه دارد. علاوه بر این، گروه‌های کربونیل به‌عنوان گروه‌های عاملی کلیدی در برهمکنش‌های لیگاند-پروتئین شناسایی شدند. با توجه به این امر می‌توان از این گروه‌های عاملی برای طراحی آنزیم‌های مصنوعی در درمان COVID-19 استفاده نمود.

واژه‌های کلیدی

Molecular docking,
SARS-CoV-2,
Artificial enzymes,
Herbal medicines Allelopathy,
Glycyrrhetinic acid

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Abstract

The COVID-19 outbreak has turned into a serious pandemic emergency, and presently is a global concern for humans worldwide. Lack of timely management and control of this disease could lead to a human catastrophe. Accordingly, various therapeutic interventions are being conducted for the COVID-19 remedy worldwide. The use of herbal medicine is one of the proposed remedy options in China and many other countries. The high homology of this viral genome with SARS (80%), and the presence of conclusive evidence of herbal medicine applications in the treatment and prevention of SARS are promising. This article focuses on the use of herbal medicine with potential application for COVID-19 remedy, and assessments of the inhibitory effects of these compounds on vital coronavirus proteins with molecular docking simulations. We also provide an opportunity to reveal the application of artificial enzymes for COVID-19 treatment. The use of artificial enzymes for the COVID-19 remedy is proposed for the first time in this study. Our molecular docking simulation results demonstrated that Glycyrrhetinic acid has an impressive inhibitory effect on all studied coronavirus proteins. Furthermore, carbonyl groups were identified as the key functional groups in the ligand-protein interactions. These can be subjected to the artificial enzyme designing for the COVID-19 remedy.

Keywords: Molecular docking, SARS-CoV-2, Artificial enzymes, Herbal medicines Allelopathy, Glycyrrhetinic acid

Introduction

Recently, the outbreak of COVID-19 has turned into a serious pandemic emergency and is a global concern for humans worldwide (Paraskevis et al. 2020; Zhang et al. 2020). With very limited facts about the current epidemiology of COVID-19, the lack of antiviral drugs or the availability of vaccines, the presence of carriers without obvious symptoms, multiple modes of transmission particularly indirect routes, high mortality rate, modern life, as well as the development of transportation systems, especially air transportation, unbridled contagion power of COVID-19, and lack of time management and control of this disease could lead to a human catastrophe (Özdemir 2020). Hence, various therapeutic interventions are currently conducted worldwide. These include oxygen therapy (Geier and Geier 2020; Jin et al. 2020; Yang et al. 2020), monoclonal antibody therapy (Venkat Kumar et al. 2020; Waldmann 2003), convalescent plasma therapy (Smith et al. 2020; Venkat Kumar et al. 2020), stem cell therapy (Golchin et al. 2020; Golchin and Farahany 2019), and drug therapy (Chen et al. 2020; Jin et al. 2020; Habibzadeh and Stoneman 2020; Smith et al. 2020; Wang et al. 2020). The use of herbal medicine has also been one of the proposed options for COVID-19 remedy in China and many other countries (Deng et al. 2020; Ling 2020; Luo et al. 2020; Mani et al. 2020; Xia et al. 2020). Herbal medicines are applied as antibacterial and antiviral treatments for a long period of time. The active compounds in plants are worthwhile sources for exploring novel drugs to treat COVID-19 due to their low toxicity, availability, and biocompatibility (Jahan and Onay 2020; Joshi et al. 2020). Furthermore, this possibility is reinforced by the high homology of the COVID-19 genome with SARS (80%) using the same host receptor and by the presence of conclusive evidence of herbal medicine applications in the treatment and prevention of SARS (Chen and Du 2020). An accurate assessment of the literature and conducted human trials regarding the use of herbal medicine in the current and past coronavirus outbreaks could provide a new approach to control and manage this expanding global catastrophe.

Wuhan City in Hubei Province of China was the first city which reported a novel cluster of pneumonia with unknown etiology. This virus affected many peoples in China and spread to other countries worldwide in a very short period of time (Paraskevis

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et al. 2020; Tang et al. 2020). Earlier, this virus was named 2019-nCoV and thereafter renamed COVID-19 by World Health Organization (WHO). Eventually, the Group of the International Committee on Taxonomy of Viruses (ICTV) proposed the name SARS-CoV-2 (Smith et al. 2020). Subsequently, on the last days of January 2020, WHO warned that the new coronavirus outbreak is a public health emergency, and this disease has entered into a pandemic status (Paraskevis et al. 2020; Zhang et al. 2020). Unfortunately, this pandemic is continuing, therefore, it is very urgent to assess all possible therapeutic agents. The main initial symptoms of COVID-19 disease are fever above 38°C, cough, muscular soreness, and dyspnea with worsening of the disease. Patients sometimes also have atypical symptoms, such as diarrhea and vomiting (Chen et al. 2020; Sun et al. 2020; Wang et al. 2020).

The coronaviruses are part of the enveloped viruses with positive-sense, single-stranded RNA genome, belonging to the coronaviridae family that mostly cause respiratory diseases in a wide range of animals as well as humans. Virologists have classified coronavirusin to the four genera α, β, γ, and δ, and the SARS-CoV-2 is a member of the β genus. Accordingly, β coronavirus envelope has four structural proteins, including Spike protein (S), envelope protein (E), membrane protein (M), and nucleocapsid protein (N), which are produced by budding through membranes of the endoplasmic reticulum or Golgi apparatus (Wu et al. 2020; Bosch et al. 2003). They may also have immune system stimulating effects (Peiris et al. 2005). The S, M, and E proteins form the viral capsid, and the N protein is involved in the genome packaging (Wu et al. 2020). Moreover, Hemagglutinin-esterase dimer protein (HE) is also one of the structural proteins of the coronavirus viral envelope. Enhancement of S protein-mediated cell entry and virus spread through the mucosa are considered activities of these proteins (Fehr and Perlman 2015) (**Fig.1A**).

In addition to structural proteins, coronaviruses have also functional proteins that are often introduced as viral enzymes. These proteins include papain-like cysteine protease (PLpro), 3C-like serine protease (3CLpro), RNA-dependent RNA polymerase (RdRp), and Helicase (Zumla et al. 2016), which are the most important enzymes involved in the transcription and replication of coronaviruses (Stadler et al. 2004).

According to the recombination analysis and phylogenetic trees, it seems that SARS-CoV-2 viruses have the highest similarity with the Pangolin-CoV viruses. However, Beta CoV/bat/Yunnan/RaTG13/2013 is more like the SARS-CoV-2 virus than to the pangolin coronaviruses (Li et al. 2020; Sun et al. 2020). Surprisingly, the human SARS-CoV-2 virus has a unique peptide (PRRA) insertion region in the spike protein, which introduces a furin cleavage motif (RRAR). This motif may be a polybasic cleavage site, leading to differentiation of SARS-CoV-2 from other coronaviruses (Li et al. 2020).

Studies have shown that the SARS-CoV-2 coronavirus accesses the host cells via its spike protein. Different proteins from host cells, which could be involved in virus entry, are reported in some recent studies. These include Angiotensin-Converting Enzyme 2 (ACE2), Sialic Acid Receptor, Transmembrane Serine Protease 2 (TMPRSS2), and Extracellular Matrix Metalloproteinase Inducer (CD147) (Sardu et al. 2020; Radzikowska et al. 2020). It also appears that catepsin B and L could participate in the virus entry. The involvement of two of these proteins, the ACE2 (Tang et al. 2020) and CD147 (Ulrich and Pillat 2020) (**Fig.1B**) is confirmed using advanced techniques.

There are currently no specific approved therapies for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Nevertheless, various therapeutic interventions are conducted worldwide such as oxygen therapy, monoclonal antibody therapy, convalescent plasma therapy, stem cell therapy, and drug therapy.

Oxygen therapy is one of the effective and important therapeutic interventions in respiratory syndromes that is designed to increase the oxygen levels in the blood. Oxygen therapy is conducted through several procedures including nasal cannula, non-invasive mechanical ventilation, invasive mechanical ventilation, and extracorporeal membrane oxygenation (ECMO) (Jin et al. 2020; Yang et al. 2020).

Monoclonal antibody therapy is a type of immunotherapy that uses monoclonal antibodies to bind certain cells or proteins. In fact, the monoclonal antibodies will stimulate the patient's immune system to attack those alien cells that are the cause of the disease (Waldmann 2003). Researchers believed that targeting the spike proteins on the SARS-CoV-2 surface by monoclonal antibodies will mitigate virus entry into the host cells and could be a promising perspective for COVID-19 remedy (Venkat Kumar et al. 2020).

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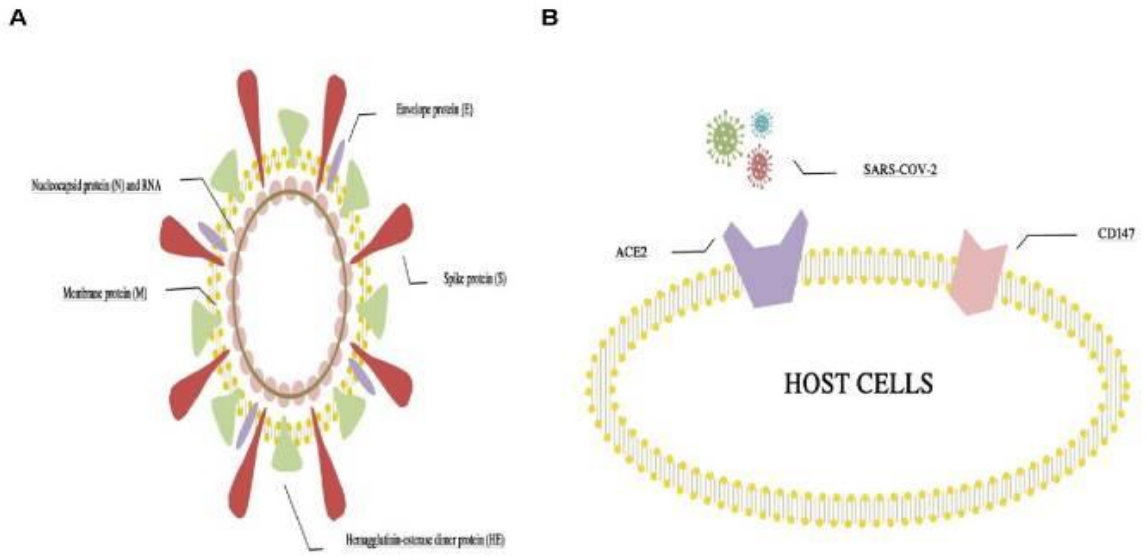

Fig. 1 The structural proteins of coronavirus envelope (**A**), and the host cell main proteins involved with virus entry (**B**).

Plasma from patients who have recovered from COVID-19 may contain antibodies to SARS-CoV-2. Clinical human trials are being conducted to assess the use of convalescent plasma for COVID-19 remedy in many countries worldwide (Smith et al. 2020; Venkat Kumar et al. 2020).

Nowadays, cell-based therapies, particularly stem cell therapies, have become a promising therapeutic achievement in incurable diseases (Golchin and Farahany 2019). Despite of all positive features of this therapy, the cell therapy has considerations and limitations. When the immune system exposed to infectious materials produces large amounts of inflammatory factors that lead to a cytokine storm. Research has revealed that the stem cell therapy can be an option for prevention of this event. The widespread application of stem cell therapy to treat COVID-19 is still at its early steps, but there is various promising reports and possibly is one of the best options for treating COVID-19 patients. However, vaccine development is still the unique way to protect from this outbreak and others (Golchin et al. 2020).

Drug therapy is a common approach to control infections such coronaviruses. Since the outbreak of SARS-CoV-2, countless drugs have been tested for its treatment. These include a wide range of compounds from antibiotics to herbal drugs. The most well-known of these are Lopinavir or Ritonavir (Jin et al. 2020; Habibzadeh and Stoneman 2020), Remdesivire (Wang et al. 2020), Azithromycin (Jin et al. 2020), Amoxicillin (Jin et al. 2020), Tocilizumab (Smith et al. 2020), Chloroquineand Hydroxychloroquine (Smith et al. 2020; Wang et al. 2020), Interferon (Chen et al. 2020; Habibzadeh and Stoneman 2020), Favipiravir (Wang et al. 2020), Enfuvirtide (Smith et al. 2020), and Corticosteroids (Chen et al. 2020; Smith et al. 2020). Unfortunately, the efficacy of these drugs has not been established for COVID-19 treatment.

China was one of the first countries faced with a coronavirus outbreak. Presently, with the passing of more than one year from the first outbreak, COVID-19 is still affecting severely all countries worldwide, while in china it is efficiently controlled. Assessment of research conducted by Chinese scientists revealed an important fact, that is traditional Chinese medicine (indeed, Chinese herbal medicine) plays a key role in SARS-COV-2 control (Luo et al. 2020). Nature is the major source of natural compounds with potential in pharmacology, which are used in traditional medicine from past to now, worldwide. Indeed, herbal medicine is the science of using medicinal plants and related compounds in medicine. Accordingly, by reviewing published articles in the field of herbal medicine usage, especially by Chinese researchers, we can see compounds that make the main components of most Chinase herbal formulas for COVID-19 treatment. These compounds include baicalein, chlorogenicacid, ephedrine, forsythiaside, glycyrrhetinicacid, kaempferol, nicotianamine, pachymicacid, patchouli alcohol, quercetin, scutellarin, and sugiol (Deng et al. 2020; Ling 2020; Luo et al. 2020; Mani et al. 2020; Xia et al. 2020) (**Table 1**). Many of these compounds are well-known allelochemicals that are produced mainly by plants

for allelopathic interactions such as chlorogenicacid (Li et al. 2010) and ephedrine (Mohsenzadeh et al. 2011). Allelochemic compounds are often highly hazardous in very low doses and have many side effects. Allelopathy is one of the defense behaviors in the plants against biotic stresses and is a sub-discipline of chemical ecology (Bakhshayeshan-Agdam and Salehi-Lisar 2020). There are numerous examples of allelopathic compounds with terrestrial and marine organism origins that promise to remedy incurable diseases (Costa et al. 2014). With increasing reliance on herbal medicine, increasing attention has been paid to allelopathy research in the pharmacology. However, it is clear that allelopathy requires advanced techniques and more research for its widespread application in pharmaceutical industry worldwide, because allelochemicals have adverse effects despite all their therapeutic benefits. Assessment of the inhibitory effects of these compounds on vital coronavirus proteins through molecular docking simulations can represent a correct view of the effective compounds, the extent of their effects, and the functional groups involved in these interactions. These evaluations can not only lead to separation of the candidate chemicals in terms of inhibitory potency and proteins multiplicity for laboratory studies, but also the introduction of effective groups in these interactions in order to design artificial enzymes to control SARS-COV-2 in the host and beyond the environment. An artificial enzyme is a synthetic organic molecule that imitates some functions of a natural enzyme. Artificial enzymes have many applications in industry, medicine, pharmacy, as well as biology, in particular in the biotechnology. These unique molecules are designed in different shapes and for different purposes. Currently, these artificial enzymes are widely used in medicine and in the treatment of various incurable diseases, such as sepsis and tumor therapy (Kuah et al. 2016).

MATERIALS AND METHODS

We have conducted an experiment to assess the inhibitory effects of selected compounds on vital coronavirus proteins (**Table 2**) with molecular docking simulation.

Table. 1 Compounds derived from herbal medicine and their features.

Name	Formula	Nature	MW	CAS No.
Baicalein	$C_{15}H_{10}O_5$	Flavone	270.24	491-67-8
Chlorogenic acid	$C_{16}H_{18}O_9$	Phenolic compounds	354.31	327-97-9
Ephedrine	$C_{10}H_{15}NO$	Alkaloid	165.23	299-42-3
Forsythiaside	$C_{29}H_{36}O_{15}$	Phenolic compounds	624.6	79916-77-1
Glycyrrhetinic acid	$C_{30}H_{46}O_4$	Triterpenoid	470.7	471-53-4
Kaempferol	$C_{15}H_{10}O_6$	Flavonol	286.24	520-18-3
Nicotianamine	$C_{12}H_{21}N_3O_6$	Non-protein amino acid	303.31	34441-14-0
Pachymic acid	$C_{33}H_{52}O_5$	Steroid	528.8	29070-92-6
Patchouli alcohol	$C_{15}H_{26}O$	Sesquiterpenealcohol	222.37	5986-55-0
Quercetin	$C_{15}H_{10}O_7$	Flavonol	302.23	117-39-5
Scutellarin	$C_{21}H_{18}O_{12}$	Flavone	462.4	27740-01-8
Sugiol	$C_{20}H_{28}O_2$	Diterpene	300.4	511-05-7

Table. 2 Protein data base IDs and molecular docking simulation conditions for the studied proteins.

Protein	PDB ID	Spacing (Å)	X (Å)	Y (Å)	Z (Å)
Viral Structural Proteins (Viral Envelope)					
S	6VXX	0.808	126	126	126
M	3I6G	0.375	126	126	126
N	6M3M	0.375	74	74	84
HE	3CL5	0.408	126	126	126
Viral Noun-Structural Proteins (Viral Enzymes)					
plpro	6WUU	0.542	90	126	106
3clpro	3VB7	0.408	126	126	126
RdRp	6M71	0.536	126	126	126
Helicase	5WWP	0.519	126	126	126
Virus Entry Receptors					
ACE	1R42	0.425	126	126	126
CD147	3B5H	0.375	126	126	70

Molecular docking simulations were performed by Autodock 4.2 (Rashtbari et al. 2017; Yekta et al. 2017) to predict the preferred binding state as well as the binding site of the compounds (as ligands) with target proteins.

All water molecules were removed by AutoDock Tools and polar hydrogen atoms, KOLLMAN atoms charge were added to the studied proteins. The docking calculations were performed using Lamarckian genetic algorithm (LGA). The Grid Box was placed at the center of proteins, and the grid map for spacing the midpoints of XXÅ and the numbers of points in the XYZ dimension are given in Table 2. After docking analysis, the lowest binding energy conformation was selected for each target and the interactions of protein complexes with compounds were also analyzed using UCSF Chimera and Discovery Studio 4.1 Client.

RESULTS AND DISCUSSION

Molecular docking results revealed that among all studied compounds, glycyrrhetinicacid with more negative binding energy, as well as its lower inhibition constants compared to other compounds, had a more stable and better binding to all SARS-COV-2 proteins (**Table 3**). The sites affected and the amino acids involved in the binding of these compounds are shown in **Fig. 2 to 13**.

Glycyrrhetinic acid is one of the allelopathic compounds of *Glycyrrhiza glabra*. This phytocompound has several therapeutic properties such as anti-bacterial, anti-fungal, and anti-viral effects, but it is carcinogenic in humans even at very low doses. Today, companies produce Licorice juice without glycyrrhetinicacid for traditional medicine usages that called LDG (Omar et al. 2012). As a result, utilizing glycyrrhetinicacid for COVID-19 patients' treatment seems not safe. Therefore, COVID-19 remedy in this way needs a safe compound that imitate glycyrrhetinic acid mimic in interaction with target proteins. This compound can be an artificial enzyme with efficacy and limited function. Recently developed artificial enzymes (nanozymes) are the best synthetic compounds that allow scientists to design targeted compounds for medical usages. Considering the key role of carbonyl groups in the studied compounds, interaction with SARS-COV-2 proteins in particular glycyrrhetinicacid, nanozymatic agents such as silver and/or gold nanoparticles (Pérez-Mirabet et al. 2012) provide desirable framework for simulation glycyrrhetinic acid mimics in the binding site. Typically, with all advantages of these nanoparticles, nanoparticle uses are also associated with several considerations; the high production costs and toxicity are the main among them.

Single-walled carbon nanotubes (SWCNTs) are another option to modulate carbonyl groups. These compounds are the hollow long cylinders that are made from one atomic sheet of carbon atoms in a honeycomb lattice. Because of their nanostructure and the strength of bonds between carbon atoms, they can be chemically modified, and can be very useful in many fields including nano-drug technology (Gebhardt et al. 2011). From the results of conducted studies, it seems that SWCNTs are safe compounds and currently, due to development of new methods, the price for each gram of material is much lower than from other nano-compounds (Saito et al. 2014; Yan et al. 2011).

Conclusions: With increasing reliance on natural compounds for COVID-19 remedy, increasing attention has been paid to the use of herbal medicine in a safe manner. The importance of artificial compounds that mimic the behavior of natural compounds will gradually be elucidated as well. This study also was an opportunity to prepare a novel platform that links the bioinformatics and nanotechnology to traditional medicine and expose the traditional medicine to modernity. The applicability of imitator compounds requires more research for widespread application in SARS-COV-2 treatment worldwide. This study is the first step in the development of such a strategy. Here we attempted to promote our idea and produce raw materials for clinical trials. We believe the results of our research can contribute to effective management and control of current and other outbreaks.

Declarations

Data Availability Statement

All data generated or analyzed during this study are included in this publish article

Conflict of Interest

The authors declare no conflict of interest.

Author Contribution

HB-A envisioned the research and HB-A and SR conducted the experiments. GD and JR assisted to experiments conducting. HB-A wrote the manuscript with JR and NS assistance. All authors read and approved the manuscript.

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Table 3 . Binding energy (ΔG) and inhibition constants (KI) of the interaction between studied compounds as ligands in molecular docking and protein complexes.

Compounds	S		M		N		HE		plpro		3clpro		RdRp		Helicase		ACE		CD147	
	ΔG	KI	ΔG	KI	ΔG	KI	ΔG	KI	ΔG	KI	ΔG	KI	ΔG	KI	ΔG	KI	ΔG	KI	ΔG	KI
Baicalein	-5.9	47.27	-6.38	21.1	-7.17	5.57	-5.31	128.44	-5.82	54.17	-7.09	6.39	-6.17	30.05	-6.64	13.53	-6.04	37.51	-6.22	27.46
Chlorogenic acid	-5.77	59.39	-5.46	99.23	-4.21	823.29	-6.93	8.29	-6.52	16.76	-5.44	102.15	-4.26	757.14	-7.24	4.96	-5.83	53.33	-7.02	7.13
Ephedrine	-4.0	117.77	-5.42	106.68	-4.93	241.7	-4.1	984.9	-5.28	134.44	-5.9	47.61	-5.33	124.73	-4.84	281.02	-6.59	14.82	-4.34	661.41
Forsythiaside	-4.6	421.36	-5.3	129.27	-3.83	89.23	-4.27	745.21	-5.85	51.32	-5.64	72.94	-5.13	172.51	-5.89	48.52	-4.65	387.12	-5.33	123.01
Glycyrrhetinic acid	-8.21	953.51	-7.01	7.33	-10.03	44.26	-7.74	2.11	-8.4	697.09	-8.32	800.57	-9.97	49.6	-11.36	4.7	-8.3	823.65	-5.87	49.81
Kaempferol	-5.15	168.39	-5.01	213.49	-6.48	17.68	-5.28	133.94	-5.68	68.17	-6.14	31.57	-5.7	66.05	-6.53	16.32	-5.61	77.73	-5.29	133.6
Nicotianamine	-3.71	1.91	-6.16	30.57	-4.5	499.86	-6.23	5.26	-4.78	312.85	-5.19	158.17	-6.15	30.8	-7.63	2.55	-6.64	13.58	-4.32	684.4
Pachymic acid	-3.77	172.2	-4.28	734.07	-5.86	50.96	-4.84	284.95	-5.2	153.58	-4.58	441.34	-5.69	67.23	-5.22	148.27	-3.43	3.04	-5.00	217.43
Patchouli alcohol	-5.08	188.77	-5.72	63.62	-5.07	193	-4.29	722.59	-5.27	137.69	-4.97	227.14	-4.77	319.98	-6.41	19.91	-4.65	393.3	-4.5	500.98
Quercetin	-3.89	1.4	-5.7	66.59	-5.94	44.45	-5.33	123.66	-3.68	2	-6.05	36.5	-6	39.71	-6.8	10.43	-5.32	125.1	-5.02	208.29
Scutellarin	-5.32	125.4	-6.11	33.25	-5.62	75.4	-5.63	74.88	-5.71	65.05	-6.3	24.22	-6.87	9.21	-6.06	36.22	-5.42	106.9	-7.43	3.55
Sugiol	-4.47	531.94	-6.18	29.46	-5.86	50.53	-5.21	152.93	-5.53	88.84	-5.65	72.64	-6.67	12.99	-7.58	2.79	-6.33	22.9	-5.59	79.32

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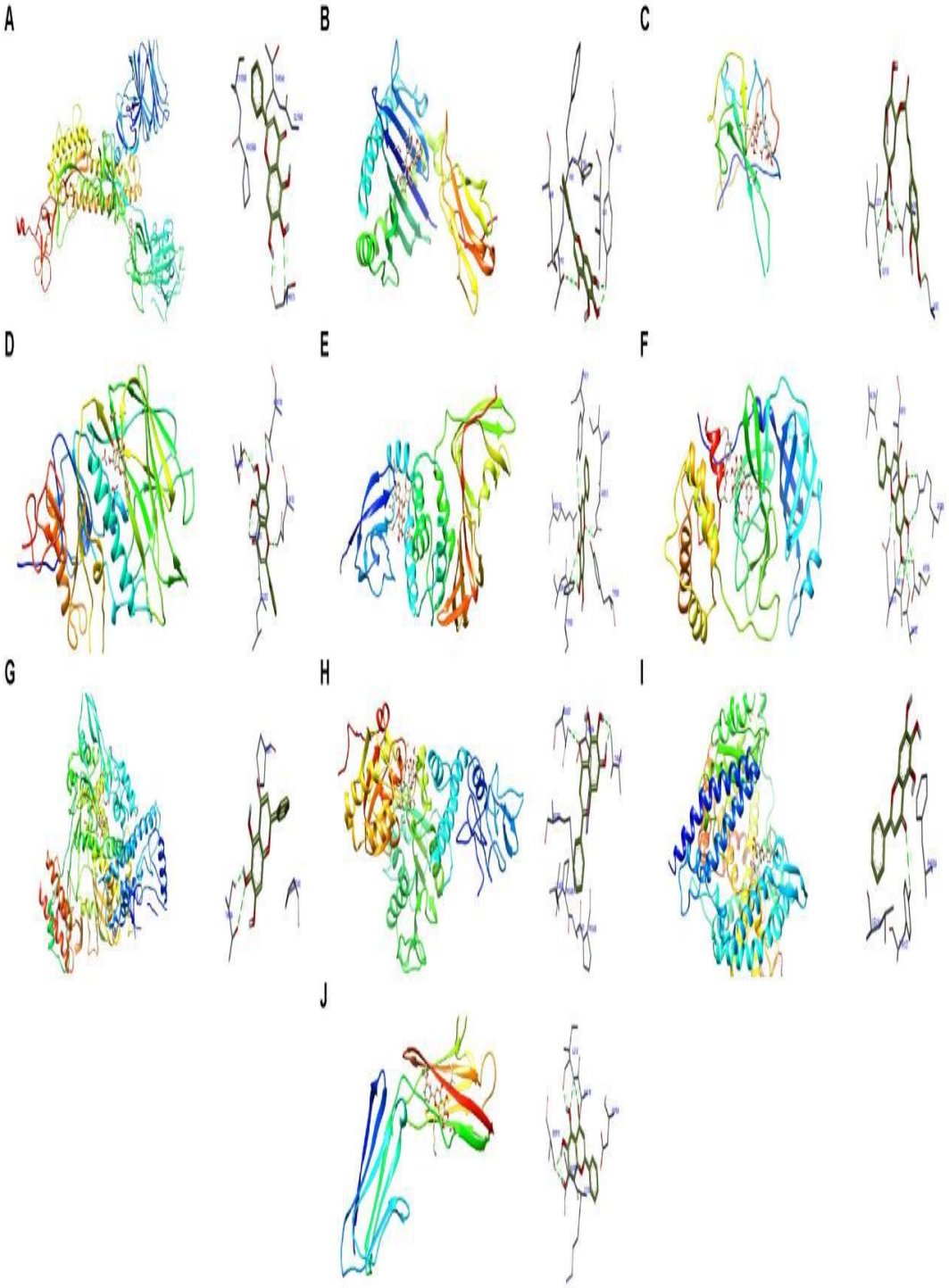

Fig. 2 Best docked conformations for Baicalein-S system (**A**), Baicalein-M system (**B**),Baicalein-N system (**C**), Baicalein-HE system (**D**), Baicalein-plpro system (**E**),Baicalein-3clpro system (**F**), Baicalein-RdRp system (**G**), Baicalein-Helicase system (**H**), Baicalein-ACE system (**I**), and Baicalein-CD147system (**J**) complexes .

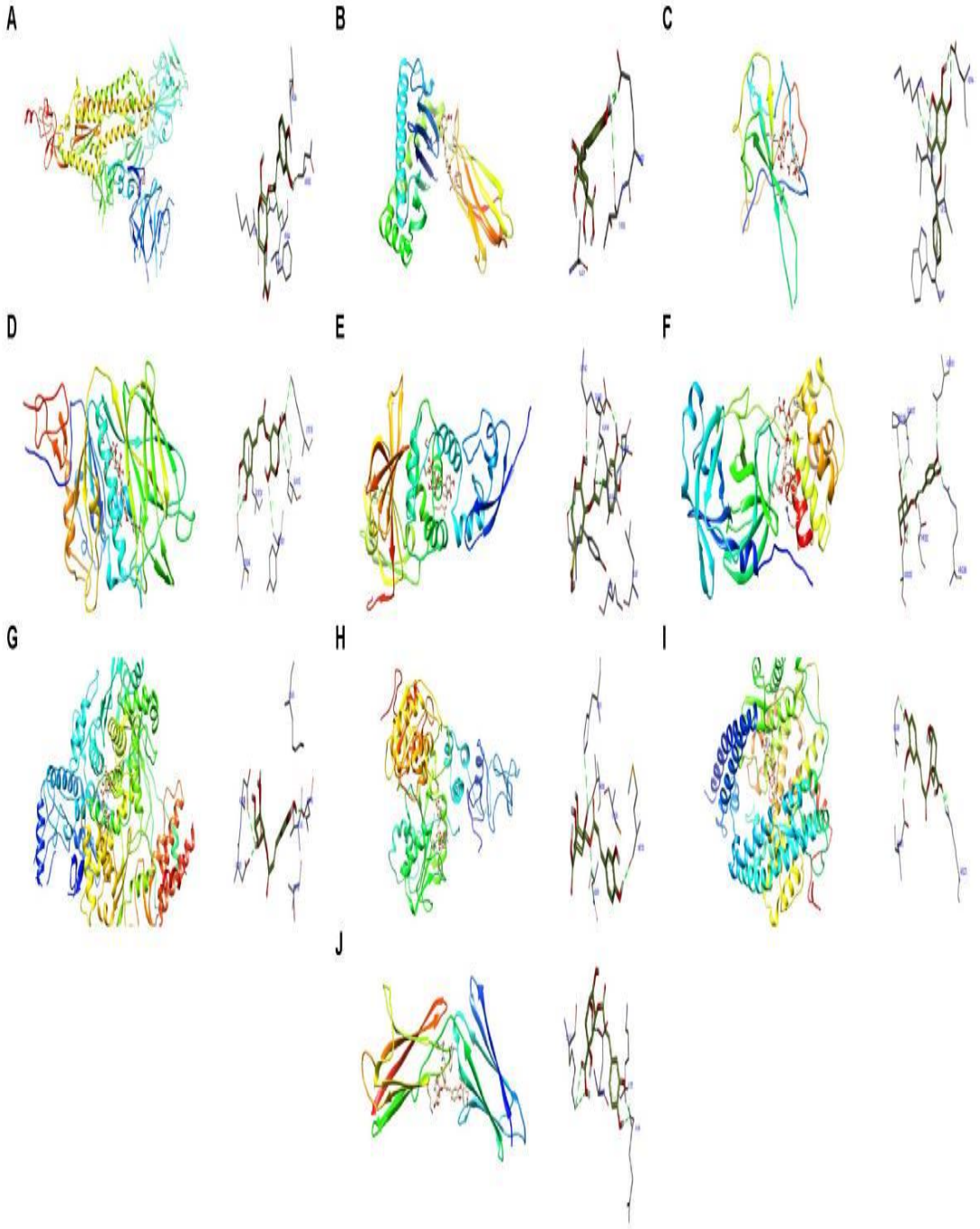

Fig. 3 Best docked conformations for Chlorogenic acid-S system (**A**), Chlorogenic acid-M system (**B**), Chlorogenic acid-N system (**C**), Chlorogenic acid-HE system (**D**), Chlorogenic acid-plpro system (**E**), Chlorogenic acid-3clpro system (**F**), Chlorogenic acid-RdRp system (**G**), Chlorogenic acid-Helicase system (**H**), Chlorogenic acid-ACE system (**I**), and Chlorogenic acid-CD147system (**J**) complexes.

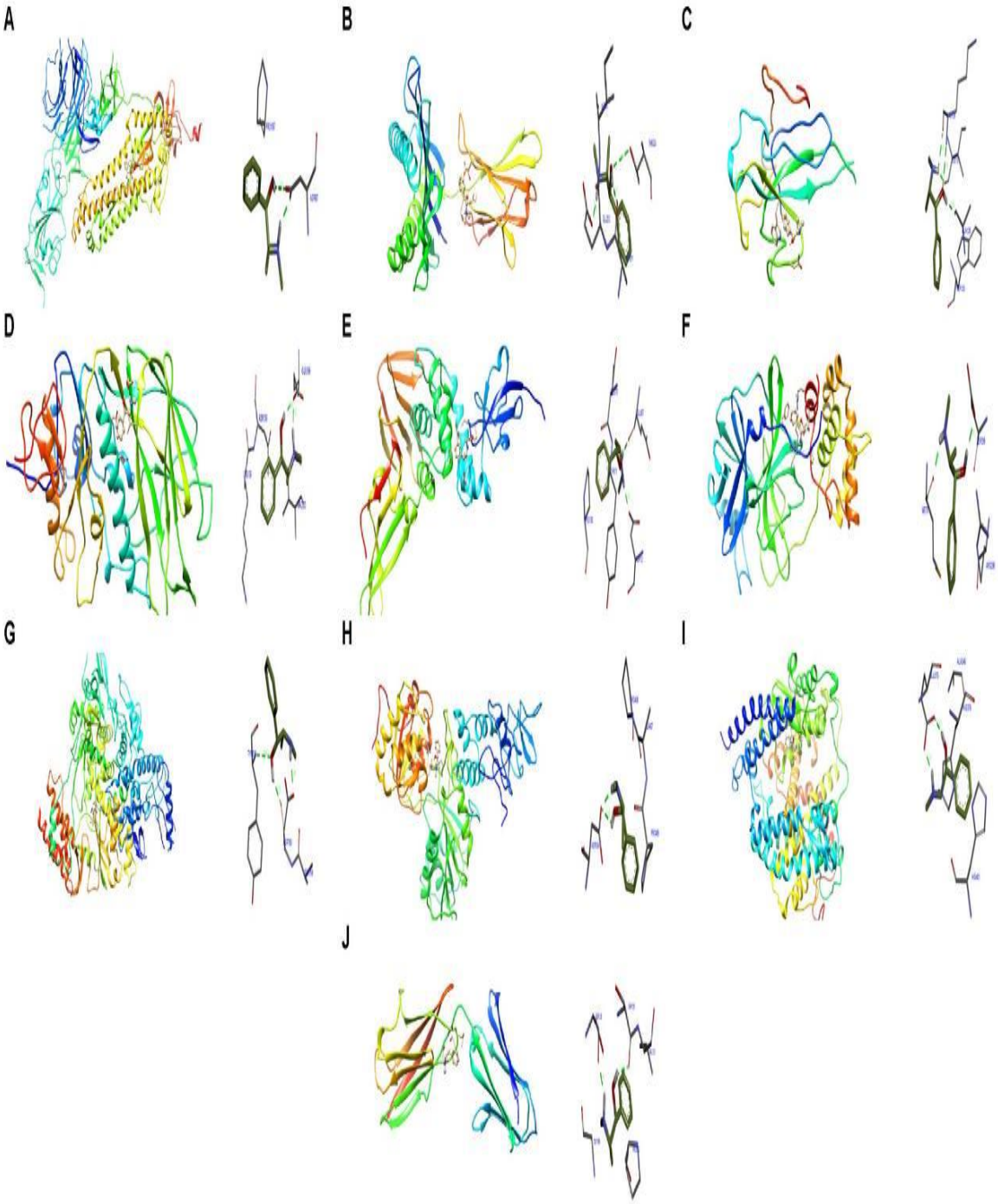

Fig. 4 Best docked conformations for Ephedrine-S system (**A**), Ephedrine-M system (**B**), Ephedrine-N system (**C**), Ephedrine-HE system (**D**), Ephedrine-plpro system (**E**), Ephedrine-3clpro system (**F**), Ephedrine-RdRp system (**G**), Ephedrine-Helicase system (**H**), Ephedrine-ACE system (**I**), and Ephedrine-CD147system (**J**) complexes.

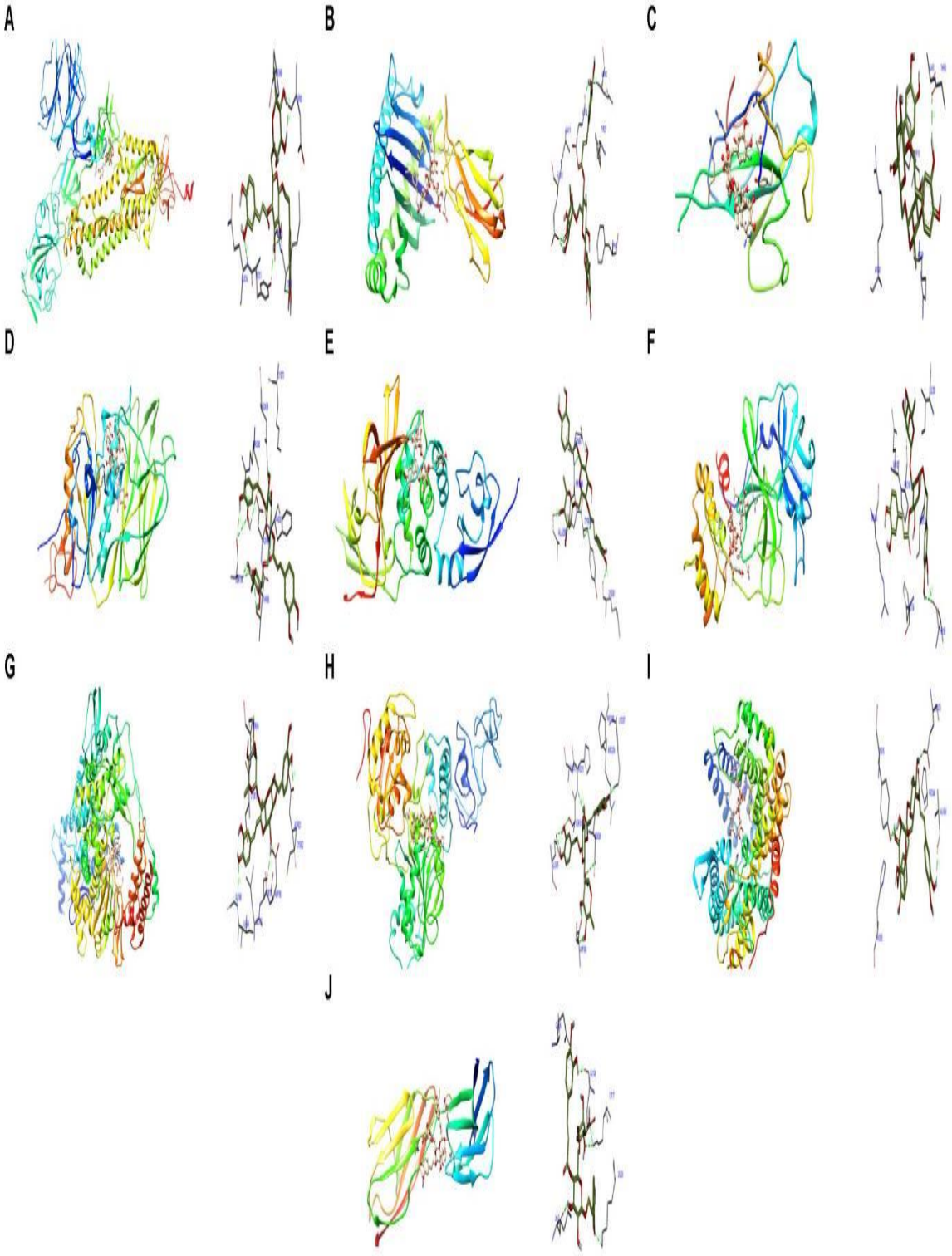

Fig. 5 Best docked conformations for Forsythiaside-S system (**A**), Forsythiaside-M system (**B**), Forsythiaside-N system (**C**), Forsythiaside-HE system (**D**), Forsythiaside-plpro system (**E**), Forsythiaside-3clpro system (**F**), Forsythiaside-RdRp system (**G**), Forsythiaside-Helicase system (**H**), Forsythiaside-ACE system (**I**), and Forsythiaside-CD147system (**J**) complexes.

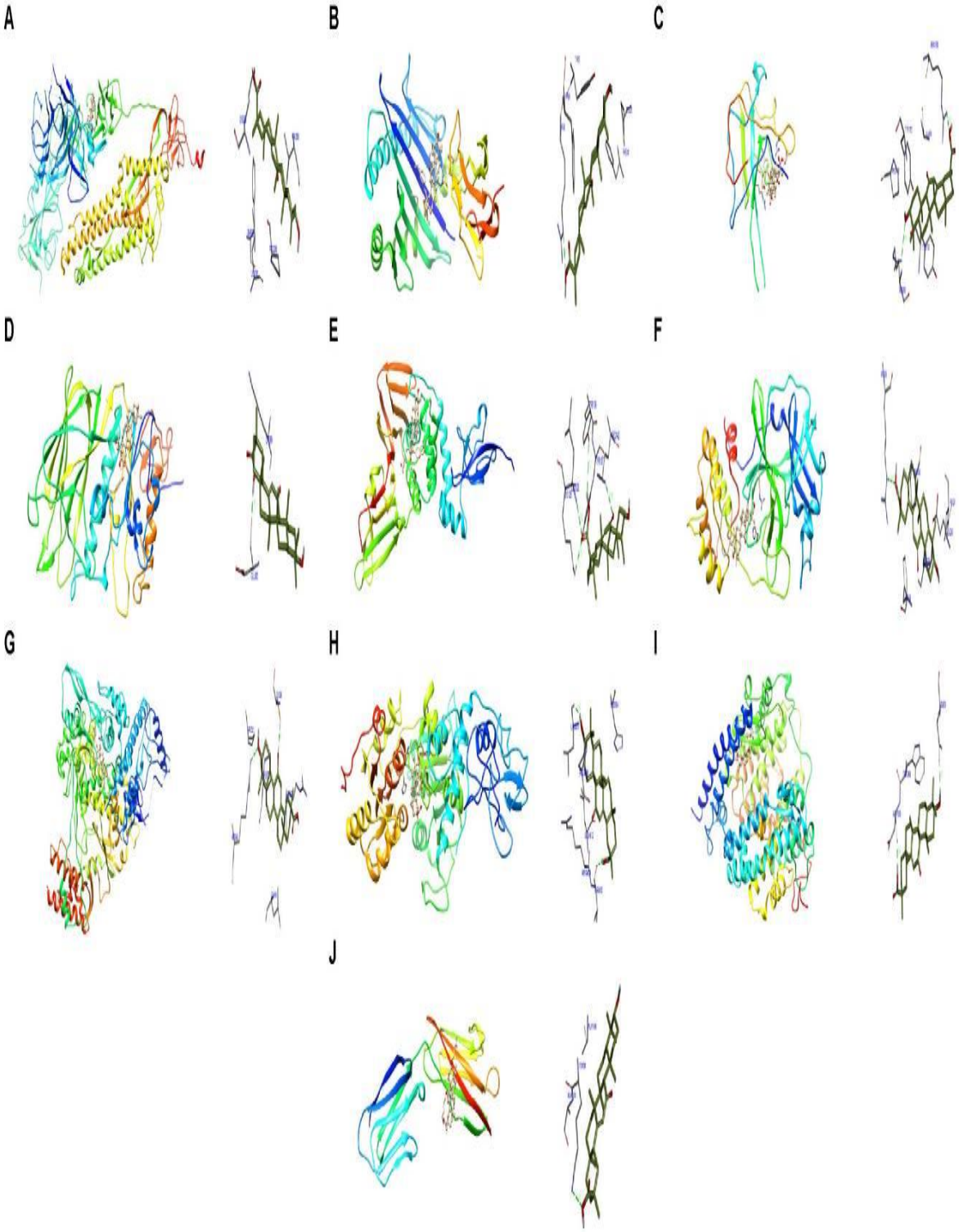

Fig. 6 Best docked conformations for Glycyrrhetinic acid-S system (**A**), Glycyrrhetinic acid-M system (**B**), Glycyrrhetinic acid-N system (**C**), Glycyrrhetinic acid-HE system (**D**), Glycyrrhetinic acid-plpro system (**E**), Glycyrrhetinic acid-3clpro system (**F**), Glycyrrhetinic acid-RdRp system (**G**), Glycyrrhetinic acid-Helicase system (**H**), Glycyrrhetinic acid-ACE system (**I**), and Glycyrrhetinic acid-CD147system (**J**) complexes.

[DOR: 20.1001.1.25885073.1400.10.1.12.2]

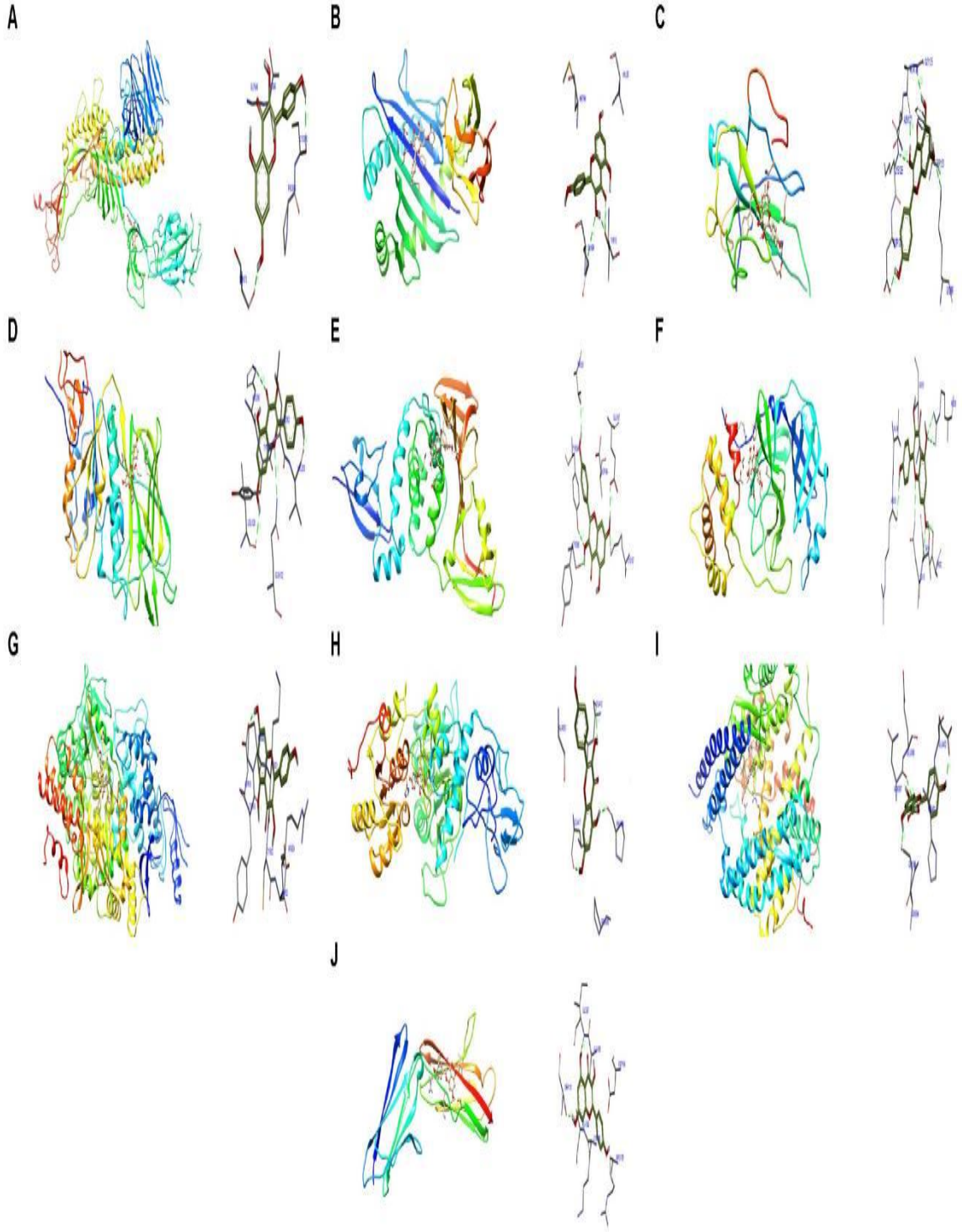

Fig. 7 Best docked conformations for Kaempferol-S system (**A**), Kaempferol-M system (**B**), Kaempferol-N system (**C**), Kaempferol-HE system (**D**), Kaempferol-plpro system (**E**), Kaempferol-3clpro system (**F**), Kaempferol-RdRp system (**G**), Kaempferol-Helicase system (**H**), Kaempferol-ACE system (**I**), and Kaempferol-CD147system (**J**) complexes.

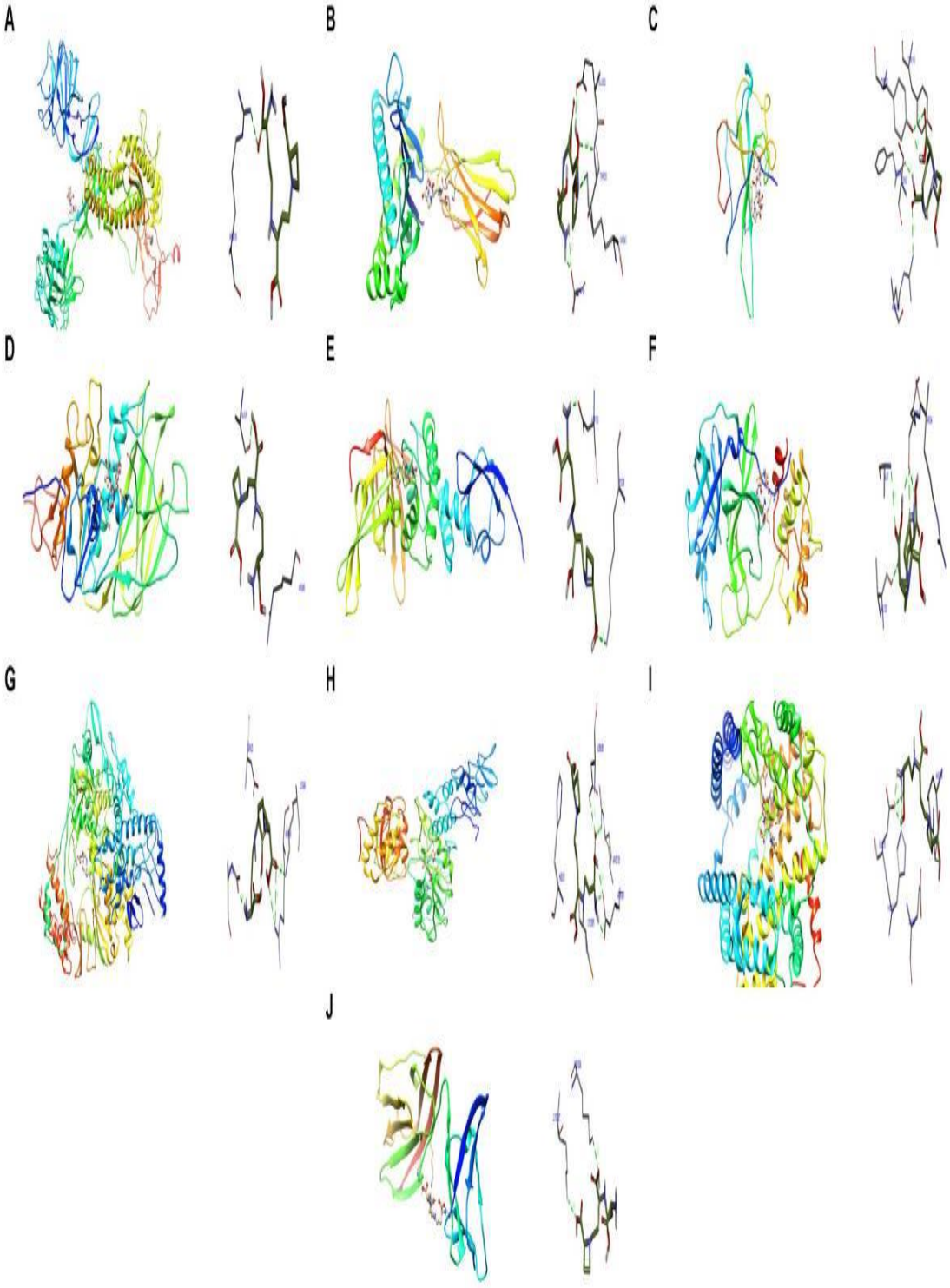

Fig. 8 Best docked conformations for Nicotianamine-S system (**A**), Nicotianamine-M system (**B**), Nicotianamine-N system (**C**), Nicotianamine-HE system (**D**), Nicotianamine-plpro system (**E**), Nicotianamine-3clpro system (**F**), Nicotianamine-RdRp system (**G**), Nicotianamine-Helicase system (**H**), Nicotianamine-ACE system (**I**), and Nicotianamine-CD147system (**J**) complexes.

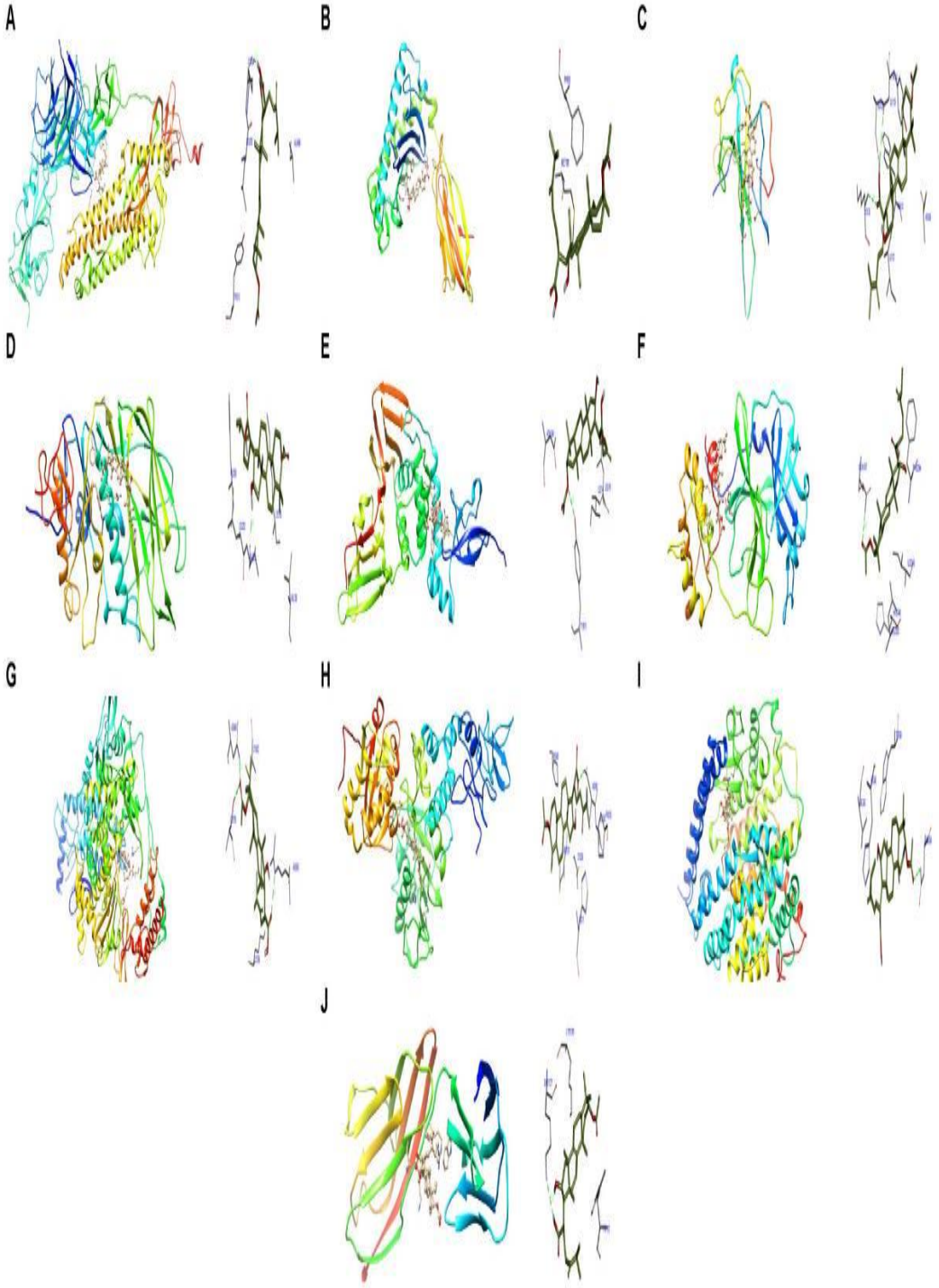

Fig. 9 Best docked conformations for Pachymic acid-S system (**A**), Pachymic acid-M system (**B**), Pachymic acid-N system (**C**), Pachymic acid-HE system (**D**), Pachymic acid-plpro system (**E**), Pachymic acid-3clpro system (**F**), Pachymic acid-RdRp system (**G**), Pachymic acid-Helicase system (**H**), Pachymic acid-ACE system (**I**), and Pachymic acid-CD147system (**J**) complexes.

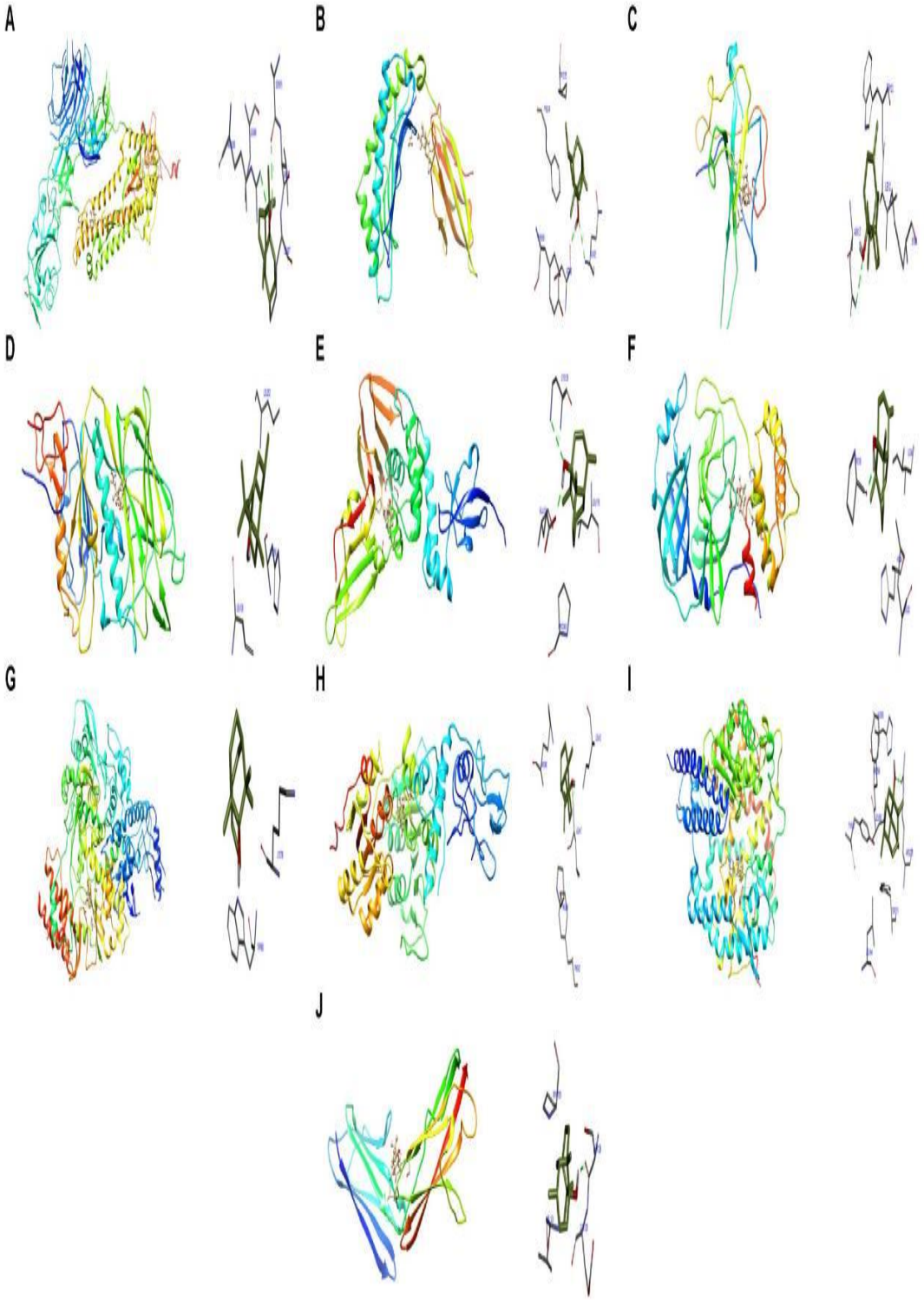

Fig. 10 Best docked conformations for Patchouli alcohol-S system (**A**), Patchouli alcohol-M system (**B**), Patchouli alcohol-N system (**C**), Patchouli alcohol-HE system (**D**), Patchouli alcohol-plpro system (**E**), Patchouli alcohol-3clpro system (**F**), Patchouli alcohol-RdRp system (**G**), Patchouli alcohol-Helicase system (**H**), Patchouli alcohol-ACE system (**I**), and Patchouli alcohol-CD147system (**J**) complexes.

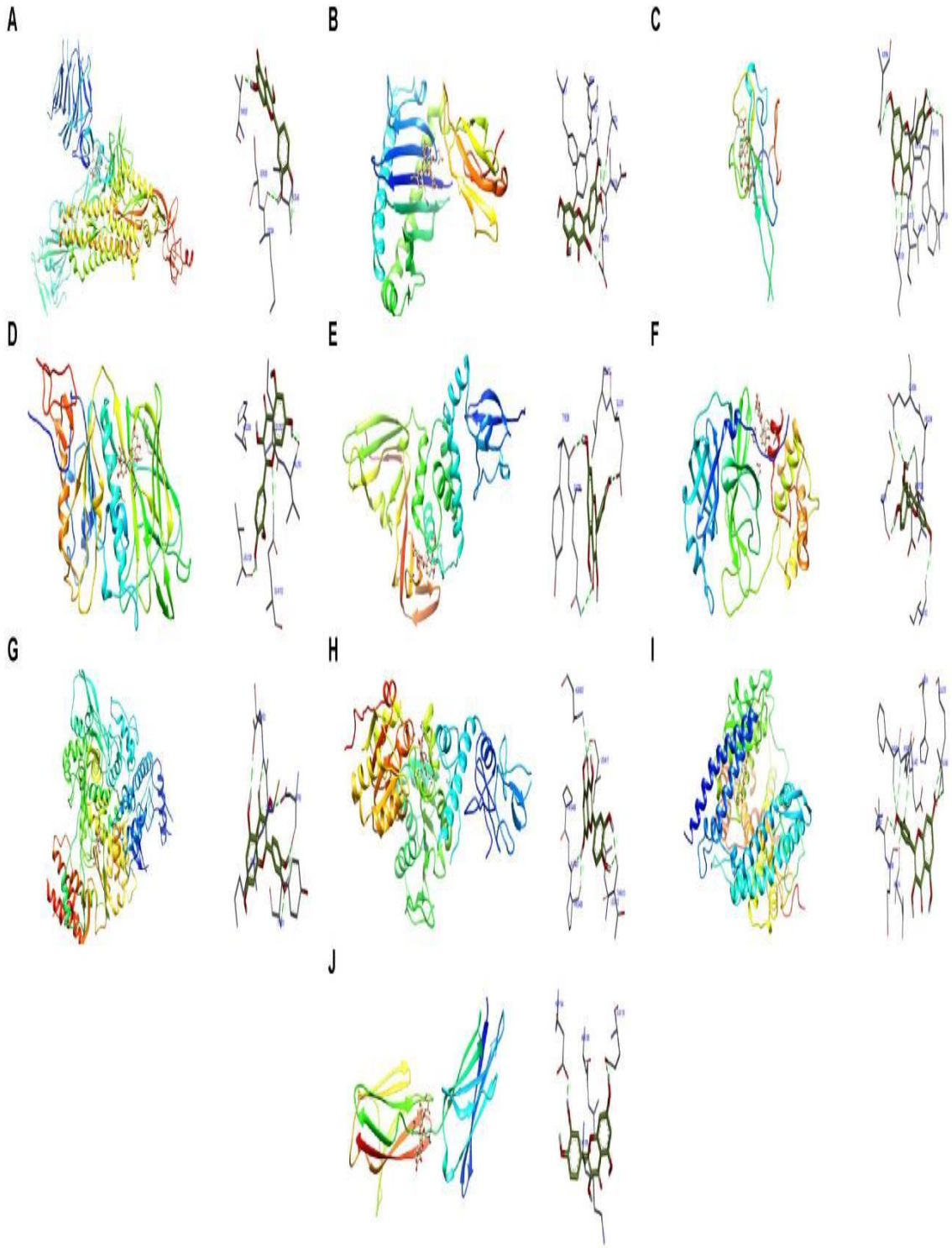

Fig. 11 Best docked conformations for Quercetin-S system (**A**), Quercetin-M system (**B**), Quercetin-N system (**C**), Quercetin-HE system (**D**), Quercetin-plpro system (**E**), Quercetin-3clpro system (**F**), Quercetin-RdRp system (**G**), Quercetin-Helicase system (**H**), Quercetin-ACE system (**I**), and Quercetin-CD147system (**J**) complexes.

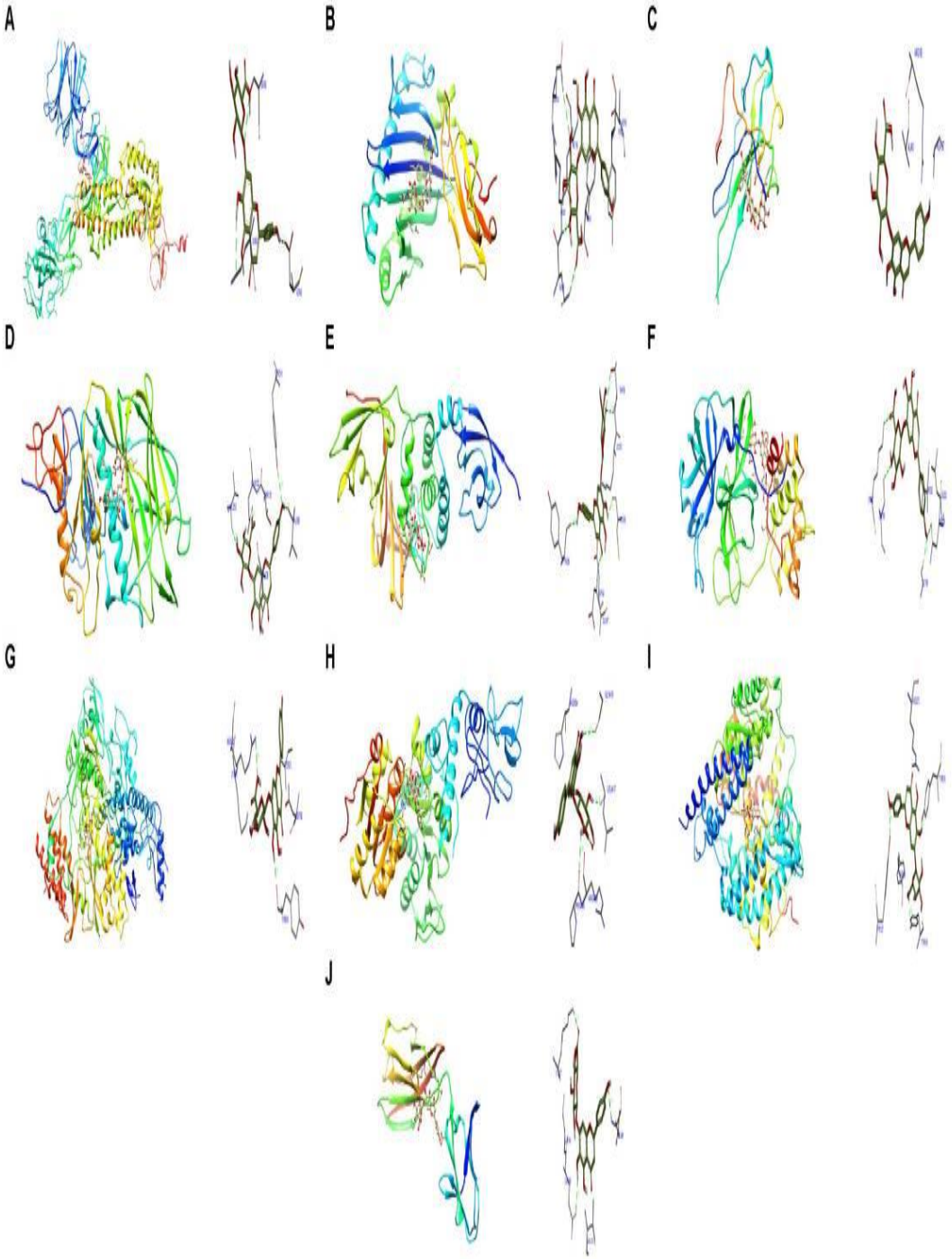

Fig. 12 Best docked conformations for Scutellarin-S system (**A**), Scutellarin-M system (**B**), Scutellarin-N system (**C**), Scutellarin-HE system (**D**), Scutellarin-plpro system (**E**), Scutellarin-3clpro system (**F**), Scutellarin-RdRp system (**G**), Scutellarin-Helicase system (**H**), Scutellarin-ACE system (**I**), and Scutellarin-CD147system (**J**) complexes.

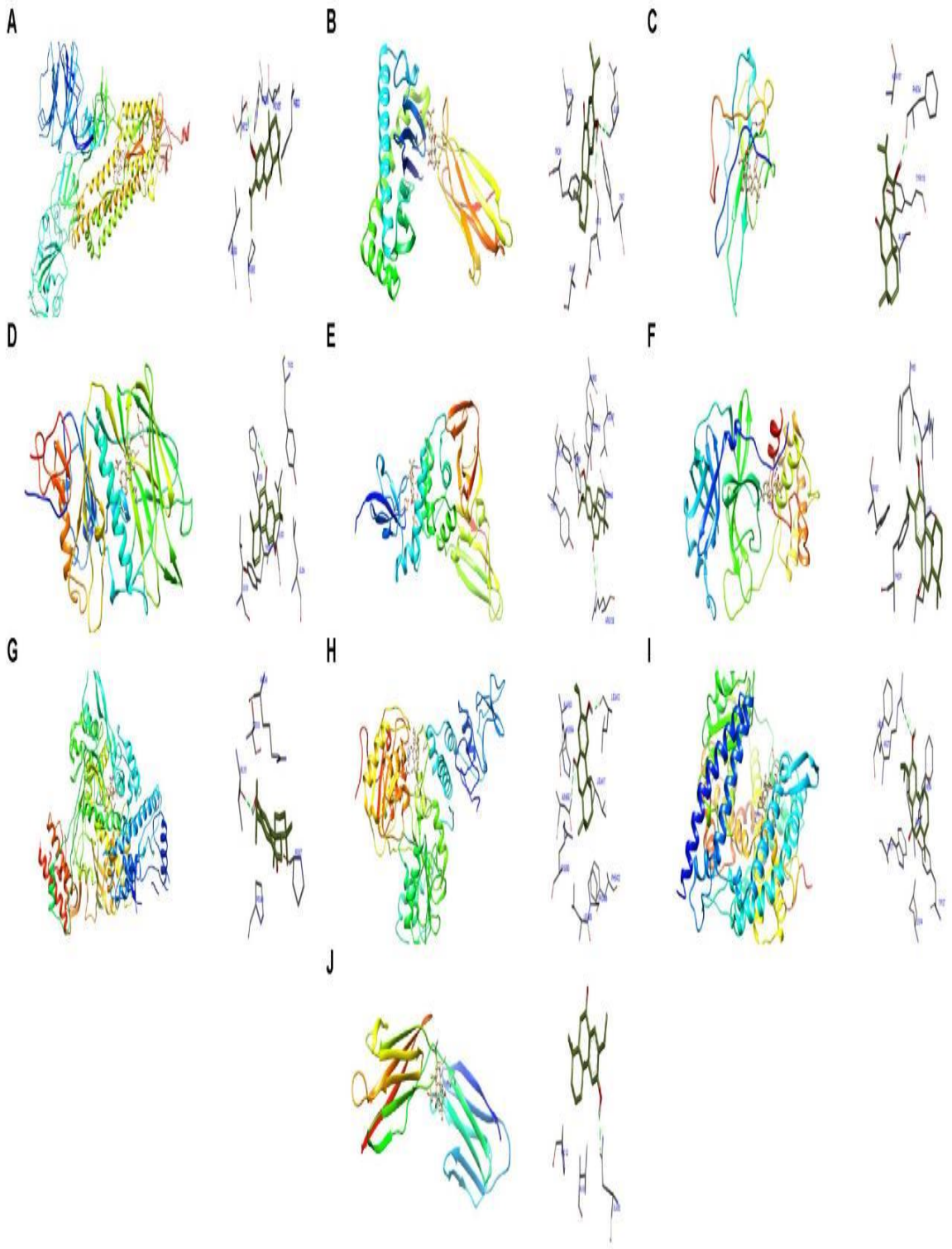

Fig. 13 Best docked conformations for Sugiol-S system (**A**), Sugiol-M system (**B**), Sugiol-N system (**C**), Sugiol-HE system (**D**), Sugiol-plpro system (**E**), Sugiol-3clpro system (**F**), Sugiol-RdRp system (**G**), Sugiol-Helicase system (**H**), Sugiol-ACE system (**I**), and Sugiol-CD147system (**J**) complexes.

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