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Teriflunomide: A possible effective drug for the comprehensive treatment of COVID-19

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has undoubtedly become a global crisis. Consequently, discovery and identification of new or known potential drug candidates to solve the health problems caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have become an urgent necessity. This current research study sheds light on the possible direct repurposing of the antirheumatic drug teriflunomide to act as an effective and potent anti-SARS-CoV-2 agent. Herein, an interesting computational molecular docking study of teriflunomide, to investigate and evaluate its potential inhibitory activities on the novel coronaviral-2 RNA-dependent RNA polymerase (nCoV-RdRp) protein, was reported. The docking procedures were accurately carried out on nCoV-RdRp (with/without RNA) using the COVID-19 Docking Server, through adjusting it on the small molecule docking mode. Remdesivir and its active metabolite (GS-441524) were used as the active references for the comparison and evaluation purpose. Interestingly, the computational docking analysis of the best inhibitory binding mode of teriflunomide in the binding pocket of the active site of the SARS-CoV-2 RdRp revealed that teriflunomide may exhibit significantly stronger inhibitory binding interactions and better inhibitory binding affinities (teriflunomide has considerably lower binding energies of −9.70 and −7.80 kcal/mol with RdRp-RNA and RdRp alone, respectively) than both references. It was previously reported that teriflunomide strongly inhibits the viral replication and reproduction through two mechanisms of action, thus the results obtained in the present study surprisingly support the double mode of antiviral action of this antirheumatic ligand. In conclusion, the current research paved the way to practically prove the hypothetical theory of the promising abilities of teriflunomide to successfully attack the SARS-CoV-2 particles and inhibit their replication in a triple mode of action through integrating the newly-discovered nCoV-RdRp-inhibiting properties with the previously-known two anticoronaviral mechanisms of action. Based on the previous interesting facts and results, the triple SARS-CoV-2/sextet COVID-19 attacker teriflunomide can further undergo *in vitro/in vivo* anti-COVID-19 assays together with preclinical/clinical studies and trials in an attempt to evaluate and prove its comprehensive pharmacological activities against the different SARS-CoV-2 strains to be effectively used in COVID-19 therapy in the very near future.

1. Introduction

On the latest days of 2019, a novel type of the coronaviruses (2019-nCoV), known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), dramatically appeared in Wuhan (China) (Hui et al., 2020). Transmission of this occult single-stranded positive nonsegmented RNA viral microbe is continuous resulting in the prevalence of the virus specific illness, coronavirus disease 2019 (COVID-19), with its main symptoms specifically present in the respiratory system of humans (reach to severe pneumonia and death in many cases) (Hui et al., 2020; Li et al., 2020). The SARS-CoV-2 has sheaths that enfold around the RNA genome (virion, which is the whole virus, is round/oval, usually polymorphic, with a diameter of approximately 50–200 nm) (Wu et al., 2020). Except for the promising investigational drugs, Cyanorona-20, CoViTris2020, ChloViD2020, and Taroxaz-104, there is no specific and effective potent drug therapy successfully recognized for COVID-19 to date at the middle of 2021 (Jiang et al., 2020; Rabie, 2021a, 2021b, 2021c, 2021d, 2021e, 2021f).

The old drugs known for their antiviral activities or any activities that hinder any stage(s) of the coronaviral life cycle are of special interests for medicinal chemists for the repurposing strategies against the COVID-19. Potent antirheumatic medicines, like hydroxychloroquine, leflunomide, and teriflunomide, are among the drugs that are under the microscope in

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this respect due to their potential antiviral activities (Ip et al., 2021; Rabie, 2021a; Mei-Jiao et al., 2019; Xiong et al., 2020). To the best of my knowledge, there is not any reported comprehensive evidence-based and/or clinical study that investigated, discussed, and proved the possibility of repurposing leflunomide and/or its active metabolite teriflunomide against the resistant COVID-19 to date.

Teriflunomide (chemically, its structure is 2-cyano-3-hydroxy-*N*-[4-(trifluoromethyl)phenyl]-2-butenamide), a once-daily orally-administered potent immunosuppressive/immunomodulatory agent, was regulatory approved in most countries of the world (including the United States and the European Union) for the effective treatment of the moderate-to-severe multiple sclerosis (MS) and some other rheumatic conditions (Bar-Or et al., 2014; Breedveld and Dayer, 2000). It was firstly identified as the major active metabolite of its parent antirheumatic drug leflunomide which is used mainly for the treatment of rheumatoid arthritis (Breedveld and Dayer, 2000). Leflunomide is converted, by the action of the *in vivo* metabolic activation, into teriflunomide which is specifically responsible for the complete biological and therapeutic actions of the parent drug (Fig. 1) (Breedveld and Dayer, 2000). The only chemical difference between the two molecules is the opening of the isoxazole ring to free and form the two pharmacologically-important moieties cyano and hydroxyl groups, of the bioactive teriflunomide molecule, instead of being embedded as less-active heteroatoms (nitrogen and oxygen atoms, respectively) in the heterocyclic isoxazole ring of the leflunomide molecule (Breedveld and Dayer, 2000; Rozman, 2002). The molecular pharmacokinetic studies revealed that the teriflunomide molecule clinically exits in two different tautomeric structures, enol/keto forms, in the blood; the enol form, in turn, exists either in the *Z*- or *E*-configuration (*Z*-*E* interconversion), with the *Z* enolic form being the most predominant structure since it is the most stable form among all the three isomers as shown in Fig. 2 (Rozman, 2002; Bohanec Grabar et al., 2009).

It is worth mentioning that there are two main concerns in the attack of COVID-19, the viral load (almost the first stage of the disease, which is mainly characterized by the speedy SARS-CoV-2 replication) and the immune response (the second stage of the disease, which is characterized by the severe immune-mediated damage) (Cantini et al., 2020). If both pivotal stages are successfully managed and inhibited, the disease will be almost significantly controlled and cured. Additionally, the success in managing any consequent, secondary, and marginal health concerns during and after the coronaviral-2 attack should also be considered. In principle, teriflunomide, with its exceptional synergistic immunomodulatory/antiviral dual mode of action, can expectedly fulfill the managing strategy for COVID-19, no matter the infecting SARS-CoV-2 particles are mutated or not (this may be a very unique characteristic property of this drug in COVID-19 treatment) (Bar-Or et al., 2014; Xiong et al., 2020). First, it can reduce and control the SARS-CoV-2 viral load, and, second, it can fight and overcome the massive cytokine immune outbreak. Recently, clinical findings proved that COVID-19 is very mild in patients treated with continuous therapeutic doses of teriflunomide and that continuing with teriflunomide therapy during SARS-CoV-2 infection and COVID-19 is very safe and even highly recommended for MS patients (Luetic et al., 2021; Capone et al., 2021; Ciardi et al., 2020). The major objective of the present research work is to search for and find any additional anti-SARS-CoV-2 activities (anti-COVID-19 mechanisms of action) of teriflunomide to assess the possibility of its clinical use as an available choice to be incorporated in the optimal therapeutic strategies and protocols designed for the effective COVID-19 treatment.

RNA-dependent RNA polymerase (RdRp) is considered one of the most interesting and effective targets for designing new medicines against the renitent SARS-CoV-2 (Rabie, 2021a, 2021c). Structurally,

Fig. 1. Teriflunomide *in vivo* generation in human from its parent drug leflunomide.

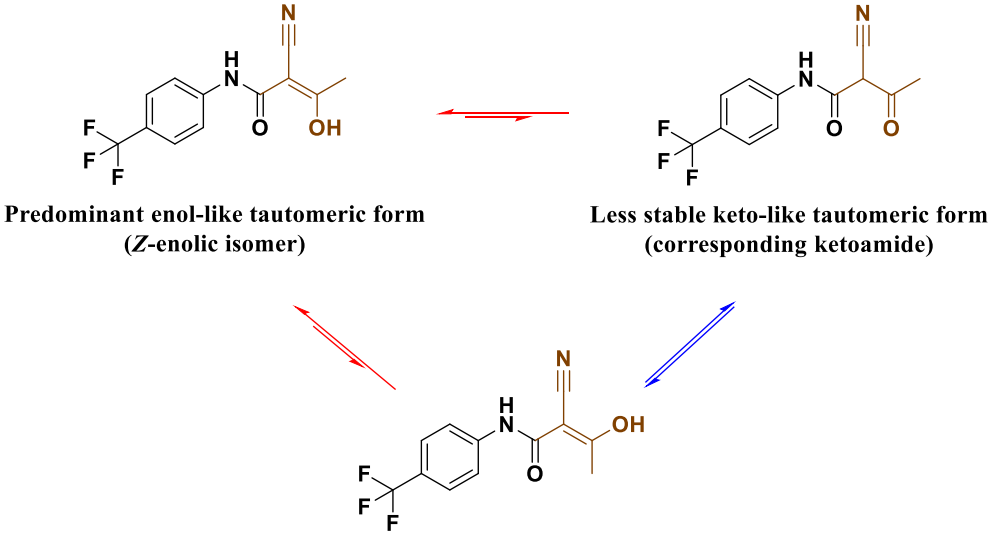


Fig. 2. Teriflunomide *in vivo* isomerization cycle in aqueous media.

RdRp is the nonstructural protein 12/7/8 (nsp12/7/8); nsp12 (chain A) is the polymerase which binds to its two major cofactors, nsp7 (chain C) and nsp8 (chains B and D) (Yin et al., 2020). It is a very pivotal enzyme in the replication and transcription of the coronaviral genome, and as a result, the potent inhibition of the performance and activities of this enzyme will significantly hinder the replication of SARS-CoV-2 and, consequently, restrict the COVID-19 infection as a whole (Rabie, 2021a, 2021c; Yin et al., 2020). The close resemblance between the structures of teriflunomide and nucleoside analogs inspired me to propose the possible action of teriflunomide to act as a potential potent inhibitor of the novel coronaviral-2 RdRp (nCoV-RdRp or, simply, CoV-RdRp). To accurately evaluate this possibility, a complete computational molecular docking study was performed using the new and well-validated molecular docking web server COVID-19 Docking Server (COVID-19 Docking Server, 2021). Remdesivir comparator protocol was used for the comparison and validation purposes using both remdesivir (a nucleotide analog) and its active metabolite (GS-441524; a nucleoside analog), since they are almost the only internationally-approved potent nCoV-RdRp inhibitors to date (Moirangthem and Surbala, 2021; Eastman et al., 2020; Yan and Muller, 2020). The results were very promising, since they revealed the strong inhibitory binding affinities of teriflunomide with the active amino acid residues of the binding pocket(s) of the nCoV-RdRp main active site (either in its complicated state with RNA or in the free state). Surprisingly, teriflunomide considerably surpasses the native ligand remdesivir together with the active metabolite GS-441524 in the negative binding energies with the nCoV-RdRp.

Based on these results and all the previous literature data and knowledge (Cantini et al., 2020; Mei-Jiao et al., 2019; Xiong et al., 2020; Teschner and Burst, 2010; Bar-Or et al., 2014; Claussen and Korn, 2012; Moon et al., 2017; Breedveld and Dayer, 2000; Capone et al., 2021; Ciardi et al., 2020; Luetic et al., 2021), my current comprehensive hypothesis can be confidently established, stating that teriflunomide can potentially act as a very effective drug candidate for the treatment of COVID-19 *via* two broad integrative efficient modes of action (i.e., a dual mode of action), each of which has three synergistic distinct mechanisms of action (Fig. 3). The first triple pathway is the novel anticoronaviral (anti-SARS-CoV-2 replication) mode of action, which includes: 1. inhibiting the coronaviral replication through interfering with the nucleocapsid tegumentation of SARS-CoV-2, which results in disruption of the SARS-CoV-2 virion assembly; 2. interfering with the coronaviral replication in the infected cells through inhibiting the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH), which plays a critical key role in the *de novo* synthesis of pyrimidine and uridine monophosphate (UMP), resulting in reduced pyrimidine *de novo* synthesis and depletion of the available pyrimidine pools, this in turn causes a large decrease in the nucleoside/nucleotide availability required for the RNA synthesis and SARS-CoV-2 proliferation (i.e., antiproliferative effect); and 3. blocking the coronaviral replication through acting as a potent direct nCoV-RdRp inhibitor (new potential effect). On the other hand, the second triple pathway is the potent immunomodulatory (immunoregulatory or anticytokine) mode of action, which includes: 1. reducing the cytokines generation, especially the interleukin 6 (IL-6), which is found to significantly contribute to the human acute respiratory distress syndrome (ARDS) in the SARS-CoV-2 infection; 2. inhibiting the immune cells activation (mainly, inhibiting the autoimmune lymphocytic activities, adhesion molecules expression, and immunoglobulin production) through disrupting the interactions with the antigen-presenting cells (by the integrin activation impairment and reduced protein aggregation); and 3. impairing the cellular (mainly, the activated autoimmune cell) reproduction and proliferation through the previously-mentioned strong action of blocking the pyrimidine *de novo* biosynthesis and, therefore, significantly depleting the intracellular pyrimidine pools. The first mode of action is concerned with the coronaviral microbe (SARS-CoV-2) particles, while the second one is especially concerned with the host (human) cells. Both triple modes of action are expected to synergistically act in a complementary/integrative and comprehensive strategic way in COVID-19 therapy.

In a word, an interesting computational molecular docking study of teriflunomide as a potential nCoV-RdRp inhibitor (anti-SARS-CoV-2 drug candidate) was reported in this current work, and thus this important research paved the way to logically and practically (i.e., clinically) establish and prove the theoretical hypothesis of the promising actions of teriflunomide to successfully treat the COVID-19 *via* attacking the SARS-CoV-2 and effectively inhibiting its replication in a triple antiviral mode of action (it acts as a potential triple attacker of the virus, and as a sextet attacker of the COVID-19 in general) through integrating the newly-discovered nCoV-RdRp-inhibiting properties (investigated herein) with the previously-known two anticoronaviral mechanisms of action (together with the original three potent immunomodulatory mechanisms of action).

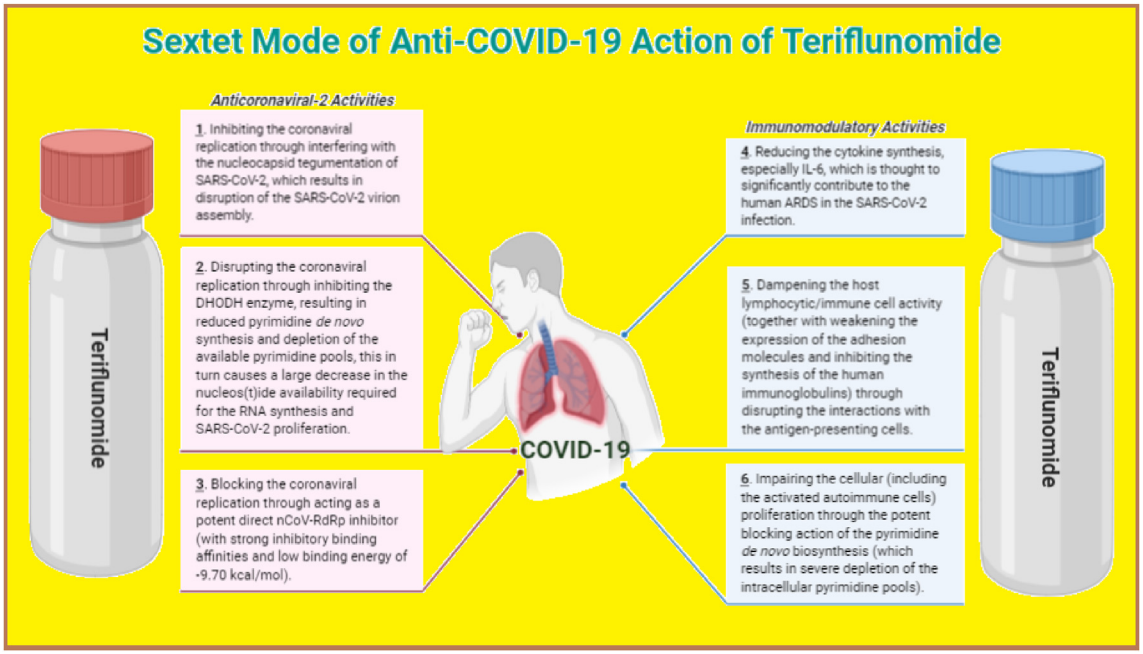


Fig. 3. Expected multimode of action of teriflunomide for the effective treatment of COVID-19 (six complementary synergistic mechanisms of anti-COVID-19 action).

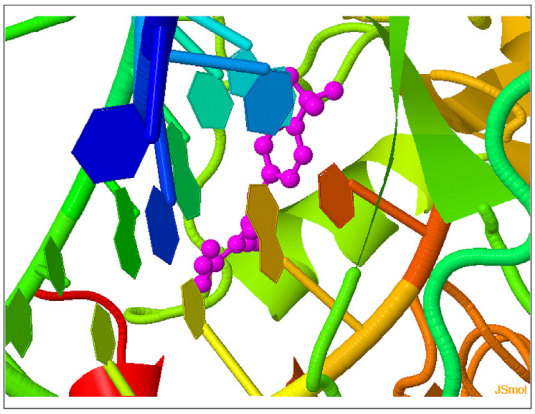
2. Materials and methods

To specifically assess the nCoV-RdRp-inhibiting properties among the overall potential anti-COVID-19 activities of the antirheumatic drug teriflunomide before its planned experimental anti-COVID-19 biological evaluation (through the *in vitro/in vivo* studies and the preclinical/clinical investigations), precise computational docking of the ligand teriflunomide molecule in the nCoV-RdRp enzyme has been primarily accomplished through utilizing the most known and credible molecular docking engines in the cheminformatics/bioinformatics field (e.g., the docking engines of GemDock, Discovery Studio, and GOLD). Trying out various programs of docking software was to certainly and convincedly reinforce and emphasize the results and to assure and guarantee the data reproducibility. The comprehensive integration of the expected key pharmacophoric characteristics with the analytical data of interaction energies detected functionally crucial amino acid residues in the active binding pockets of the of SARS-CoV-2 RdRp along with the *in silico* expected prevalent inhibitory binding modes with the very potent standard reference compounds (e.g., remdesivir and GS-441524). Computationally, the molecular docking outcomes were very promising and encouraged me to use the newly-designed web docking servers (especially programmed and founded after the COVID-19 pandemic, in 2020, for the immediate assessment of the potential anti-COVID-19 activities of the recommended and potential ligands) for the specific and direct accurate docking of the SARS-CoV-2 RdRp structure, thus the COVID-19 Docking Server was particularly used (COVID-19 Docking Server, 2021).

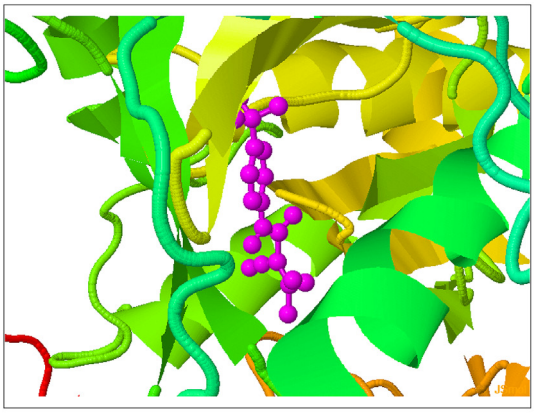
The used COVID-19 Docking Server application (AutoDock Vina is employed as the main molecular docking engine in this new computational server) is a web-based software for interactively docking small molecules/peptides/antibodies against the possible COVID-19 protein targets to anticipate the binding modes between the SARS-CoV-2 targets and the potential ligands in order to screen and assess the anti-COVID-19 actions of these ligands (i.e., the program furnishes an open and free interactive up-to-date tool using a highly accurate information-based scoring function for evaluating the candidate binding poses for the specific prediction of the COVID-19 target-ligand interactions and the next drug discovery for the COVID-19 therapy) (COVID-19 Docking Server, 2021). According to this interactive server, the structures of all the functional and structural protein targets (enzymes, receptors, etc.) engaged in the replication/reproduction life cycle of the coronavirus 2 were either directly collected or indirectly constructed based on their known homologs of the entire family of coronaviruses (by utilizing the homology modeling module of Maestro 10, website: www.schrodinger.com), and completely got ready for direct docking on this web-based software (COVID-19 Docking Server, 2021). The 3D protein structure of the nCoV-RdRp (nsp12/7/8) cocrystallized in a complex with RNA and the triphosphate form of remdesivir (RTP) was obtained from the Protein Data Bank (PDB) database with the code of 7BV2 (Yin et al., 2020; Kirchdoerfer and Ward, 2019). Thus, two major active sites for small molecule docking of nCoV-RdRp were recognized: the RTP binding site (RTP site, i.e., for RdRp-RNA or RdRp with RNA), and the RNA binding site (RNA site, i.e., for RdRp alone or without RNA) (COVID-19 Docking Server, 2021). For docking of just one small molecule each time, the "Docking" mode box as the computational type must be particularly chosen for each specific target (this is the used option in the current state). To obtain the most precise results, an average exhaustiveness option of "12" was selected. Teriflunomide was the tested ligand, while remdesivir and GS-441524 were used as the positive reference control ligands. The resulted binding complexes were clearly visualized in 3D models by JSmol. The data outputs of the COVID-19 Docking Server include both the binding free energy score values (in kcal/mol) and rescoring binding affinity random forest (RF) score values (expressed as pKd "= −log (Kd)") (Kd is the dissociation constant which is commonly used to quantify the strength with which a ligand binds to a specific protein. This important equilibrium constant measures the tendency of a specific protein-ligand complex to separate into its constituent components; it is used herein to describe the degree of tightness of proteins to their binding ligands "binders". That is, by interpreting complexes whose components are more likely to dissociate "high dissociation

Table 1
Score values of the two computationally-predicted anti-SARS-CoV-2 properties (against SARS-CoV-2 RdRp-RNA and SARS-CoV-2 RdRp, respectively) of the target teriflunomide and its two potent antiviral references (remdesivir and GS-441524), respectively, using the COVID-19 Docking Server methodology (the table shows the top docking model score value "ranked 1", i.e., the top binding mode score value or the least predicted binding free energy value, in kcal/mol, together with its corresponding highest binding affinity RF score value, expressed as pKd value, for each compound with each target RdRp site of the two ones).

Classification	Compound Name	*Top Pose Score Values for Docking of SARS-CoV-2 RdRp*			
		nCoV-RdRp-RNA (RTP Site)		nCoV-RdRp (RNA Site)	
		Score Value (kcal/mol)	RF Score Value (pKd)	Score Value (kcal/mol)	RF Score Value (pKd)
Tested Drug	**Teriflunomide**	**−9.70**	**6.99**	**−7.80**	**5.66**
Reference	**Remdesivir**	**−8.30**	**5.38**	**−7.10**	**5.27**
Drugs	**GS-441524**	**−9.10**	**6.47**	**−7.00**	**4.86**



a



b

Fig. 4. Screenshots of COVID-19 Docking Server outputs of the top predicted binding model of the docking of teriflunomide molecule (colored pink) in: (a) SARS-CoV-2 RdRp-RNA "RTP site" (PDB code: 7BV2; colored with other various colors; Cartoon Style). (b) SARS-CoV-2 RdRp "RNA site" (PDB code: 7BV2; colored with other various colors; Cartoon Style). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

constants" as loosely bound "low binding affinities" and vice versa. In brief, higher pKd values reflect exponentially greater binding affinities). The detailed results of all the estimations for the top (best) model in each case are shown in Table 1 (Fig. 4a and b and Fig. 5a–d demonstrate the docking output images, respectively).

After performing the COVID-19 Docking Server methodology, the resulted structures of nCoV-RdRp-teriflunomide, nCoV-RdRp-remdesivir, and nCoV-RdRp-GS-441524 complexes of the best models were further three-dimensionally analyzed (3D visualization) for additional validation and accurate characterization using the internationally-trusted automated Protein-Ligand Interaction Profiler (PLIP) web server (Protein-Ligand Interaction Profiler (PLIP), 2021; Adasme et al., 2021). The obtained output images of these analyses are respectively demonstrated in Fig. 6a–c, while the detailed data for nCoV-RdRp-teriflunomide interactions are specifically demonstrated in the screenshotted table of Fig. 7.

3. Results and discussion

The perception of the SARS-CoV-2 protein-ligand interactions exemplifies a very critical key challenge in drug discoveries for the management and treatment of COVID-19. The primary and fundamental theoretical prediction of the nCoV-RdRp-inhibiting properties of the newly-repurposed antirheumatic drug teriflunomide quite assists us to get an overview of the comprehensive anti-COVID-19 activities of this target compound. This computational expectancy also aids us to obtain a detailed conception about the major mode of anti-COVID-19 action of teriflunomide together with the drug degrees of effectiveness and potency. The validated docking procedures were sufficient for that, since they were performed in the nCoV-RdRp in each of its two states, the complex-with-RNA state and the free one.

On close checking of the score values of nCoV-RdRp-RNA and nCoV-RdRp dockings using the COVID-19 Docking Server (shown in Table 1), it is clearly observed that teriflunomide is specifically ranked first in its inhibitory binding affinities and potencies with binding free energies of −9.70 and −7.80 kcal/mol and with corresponding rescoring RF values of pKd of 6.99 and 5.66, respectively. The binding affinities of teriflunomide considerably exceed those of the two bioactive references remdesivir (it has binding free energies of −8.30 and −7.10 kcal/mol, and RF score values "expressed as pKd" of the inhibitory binding affinities of 5.38 and 5.27, respectively) and GS-441524 (it has binding free energies of −9.10 and −7.00 kcal/mol, and RF score values "expressed as pKd" of the inhibitory binding affinities of 6.47 and 4.86, respectively). Teriflunomide powerfully binds to the SARS-CoV-2 RdRp (with RNA) in their complex (i.e., teriflunomide molecule forms a very stable complex with the SARS-CoV-2 RdRp-RNA) with a relatively low binding free energy which is the lowest among all (i.e., significantly lower than the binding free energies of both remdesivir and GS-441524 in their complexes with the coronaviral-2 RdRp-RNA). GS-441524 and its parent potent antiviral remdesivir come second and third, respectively, in their relative inhibitory binding, potency, and efficacy on nCoV-RdRp, therefore, the results clearly express the high superiority of the antirheumatic teriflunomide over both of them as a potent anti-COVID-19 candidate agent. For more explanation, Fig. 4a and b and Fig. 5a–d show the outputs of the COVID-19 Docking Server top/best predicted binding model/mode of docking of nCoV-RdRp-RNA and nCoV-RdRp with the potential inhibitor teriflunomide and the two potent references remdesivir and GS-441524, respectively. These promising results of the predicted binding modes of teriflunomide with the protein enzyme nCoV-RdRp (with/without RNA) significantly comply with and uphold the presently-proposed mechanism of anti-COVID-19 action of teriflunomide in this study (see Introduction, Fig. 3).

Interestingly, this binding activity of the teriflunomide molecule makes it more stabilized and firm in the relevant enzymatic binding

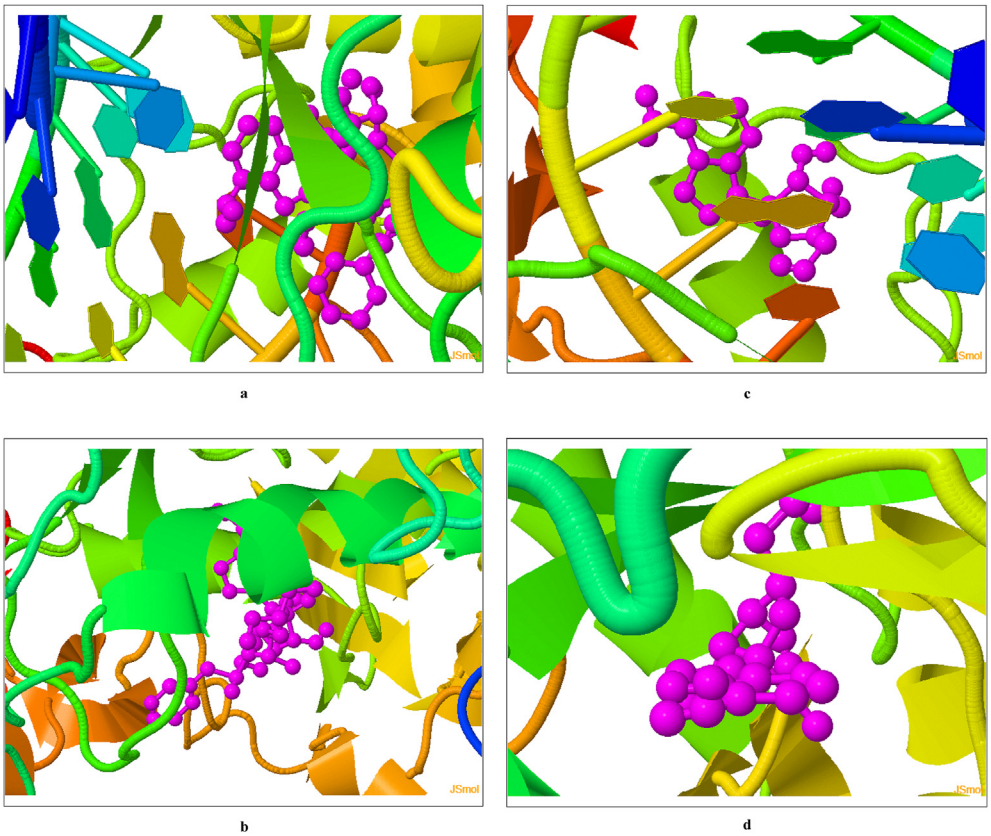


Fig. 5. Screenshots of COVID-19 Docking Server outputs of the top predicted binding model of the docking of: (a) Remdesivir molecule (colored pink) in SARS-CoV-2 RdRp-RNA "RTP site" (PDB code: 7BV2; colored with other various colors; Cartoon Style). (b) Remdesivir molecule (colored pink) in SARS-CoV-2 RdRp "RNA site" (PDB code: 7BV2; colored with other various colors; Cartoon Style). (c) GS-441524 molecule (colored pink) in SARS-CoV-2 RdRp-RNA "RTP site" (PDB code: 7BV2; colored with other various colors; Cartoon Style). (d) GS-441524 molecule (colored pink) in SARS-CoV-2 RdRp "RNA site" (PDB code: 7BV2; colored with other various colors; Cartoon Style). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

pocket(s) of nCoV-RdRp (based on the results of the present molecular docking research, teriflunomide molecule potently interacts with the pivotal amino acid residues in one of the active binding pockets of the SARS-CoV-2 RdRp enzyme with considerable number of hydrogen bonds, i.e., with significant blocking binding strength), and therefore, potentially more efficient in blocking and hindering the RdRp performance and bioactivity than the two tested reference compounds. PLIP analytical and characterization results (Fig. 6a–c and Fig. 7) clearly revealed the superiority of teriflunomide over remdesivir and its metabolite as a potential nCoV-RdRp inhibitor, since teriflunomide molecule strongly binds to one or more of the computationally-predicted active site pockets of the coronaviral-2 polymerase nCoV-RdRp with higher number of hydrophobic interactions, hydrogen bonds, π–π stackings, and/or other types of interactions as compared to remdesivir and GS-441524 molecules. The three molecules bind to active amino acid residues of similar and/or close regions of one of the polymerase expected active sites, but, when the two reference molecules are compared to the teriflunomide molecule, we will interestingly observe that remdesivir molecule interacts by less number of hydrogen bonds and almost by negligible hydrophobic and π-stackings interactions, while GS-441524 molecule, on the other hand, interacts approximately by the same number of hydrogen bonds and almost by no hydrophobic and π-stackings interactions. The detailed expected interactions of teriflunomide molecule with nCoV-RdRp macromolecule are tabulated in Fig. 7 (according to PLIP server visualization).

The chemical structure of teriflunomide specifically displays higher degrees of balanced conformational and orientational flexibilities as compared to the structures of the used references remdesivir and GS-441524, this is mainly due to the relatively higher ratio of the number of rotatable bonds to the number of rigid bonds, and, in addition, the lower number of rings (only one ring) in teriflunomide molecule when compared to the two reference molecules (more rigid structures). These exceptional flexibilities of teriflunomide chemical structure are evidently observed in the resulted top docking poses in nCoV-RdRp-RNA and nCoV-RdRp target proteins as previously shown in Fig. 4a and b, respectively. Teriflunomide molecule has much simpler structure with lower molecular weight and volume if it is compared to the structures of both used references. The highly-balanced flexibility of the uncomplicated structure of teriflunomide is crucially needed for outstanding and perfect positioning of the drug molecule to be extremely superimposable in the active binding pocket and cavity of the COVID-19 polymerase protein (i.e., required for the extreme lock-and-key positioning) (Rabie, 2021e). This, in turn, results in more proper and sufficient (i.e., potent) inhibition of the replication activities mediated or controlled by the SARS-CoV-2 RdRp. Foreseeably, the highly-balanced considerable flexibility of teriflunomide molecule significantly increases its potential biological ability and activity to act as a very potent anti-COVID-19 agent.

Additionally, the possibility that teriflunomide molecule may undergo intracellular metabolism into less active forms by human cellular enzymes is extremely limited or even totally excluded, since, biologically and clinically, teriflunomide is almost the final active metabolite that could be biogenerated and obtained from the parent antirheumatic leflunomide. Thus, teriflunomide has an extra advantage, over remdesivir and most other investigated anti-COVID-19 drug candidates, of being nonconvertible to other inactive or less active forms *in vivo*. It is worth noticing that teriflunomide has significant chemical structural similarity with many under-investigation anti-COVID-19 drug candidates, such as remdesivir, Cyanorona-20 (Rabie, 2021a, 2021b), GS-441524, and favipiravir (Cai et al., 2020), since it has the same key and principal anti-nCoV-RdRp structural elements and features (e.g., cyano group, hydroxyl group(s), fluoro group(s), nitrogenous moieties, ketonic moiety/moieties, phenyl moiety, and aliphatic side chains) in relatively similar or analogous positions as almost all of these investigational anti-COVID-19 drugs (Fig. 8). The collective results of the current research are expected to pave the way for medicinal chemists, pharmacologists, clinical investigators, and physicians to start their deep and extensive biological and clinical studies/trials to investigate and evaluate the significant and efficient abilities of teriflunomide to inhibit and hinder the targeted coronaviral-2 reproduction/replication processes.

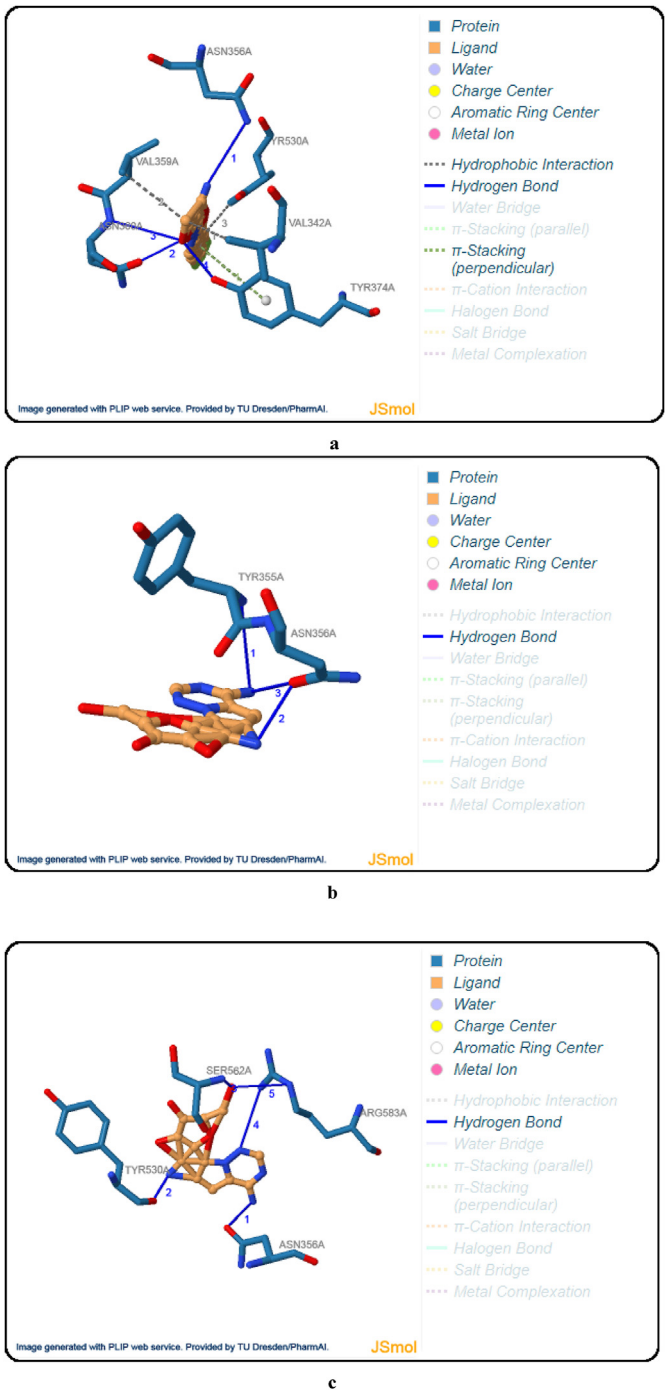


Fig. 6. PLIP output images resulted from 3D visualization of the main physicochemical interactions of the top predicted binding model (previously obtained from the COVID-19 Docking Server) of the docking of nCoV-RdRp (without RNA) with: (**a**) Teriflunomide molecule. (**b**) Remdesivir molecule. (**c**) GS-441524 molecule.

Hydrophobic Interactions

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	342A	VAL	3.99	8811	2148
2	359A	VAL	3.90	8811	2285
3	530A	TYR	3.38	8815	3650

Hydrogen Bonds

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Side chain	Donor Atom	Acceptor Atom
1	356A	ASN	3.26	4.03	136.69	✓	✓	2262 [Nam]	8808 [N1]
2	360A	ASN	2.52	3.05	113.81	×	✓	8812 [Nam]	2293 [O2]
3	360A	ASN	2.87	3.83	166.33	✓	×	2287 [Nam]	8810 [O2]
4	374A	TYR	1.80	2.58	138.96	✓	✓	2407 [O3]	8810 [O2]

π-Stacking

Index	Residue	AA	Distance	Angle	Offset	Stacking Type	Ligand Atoms
1	374A	TYR	5.22	81.80	1.95	T	8813, 8814, 8815, 8816, 8821, 8822

Fig. 7. A screenshot of the PLIP output table which enumerates and demonstrates the expected main interactions of teriflunomide molecule with nCoV-RdRp macromolecule in details.

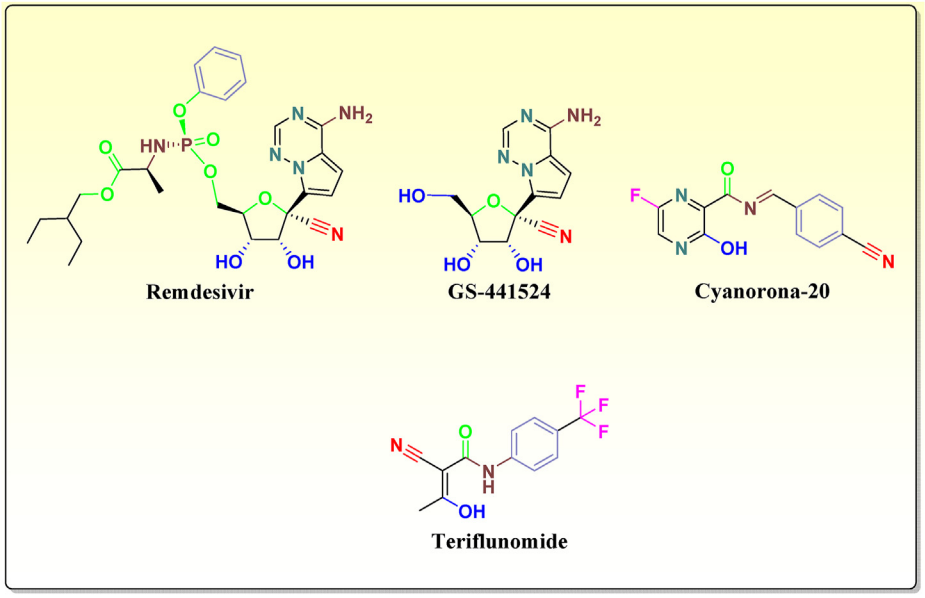


Fig. 8. Significant structural similarities of the key anti-nCoV-RdRp functional moieties of teriflunomide and its preceding investigational anti-COVID-19 candidate agents.

4. Conclusions

Comprehensively, in the light of the proved potent antiviral/immunomodulatory activities of teriflunomide, together with the promising computational docking results of the current detailed ligand-protein interaction study, we can conceptually establish a strong starting base for the promising abilities of teriflunomide to successfully strike the SARS-CoV-2 particles of different strains and combat their accompanying immunogenic cytokine storm/inflammatory condition in humans, thus providing an effective dual drug treatment for COVID-19. Teriflunomide significantly inhibits SARS-CoV-2 RdRp with encouraging low inhibitory binding energies, which reach about −9.70 kcal/mol, and strong

inhibitory binding interactions (comparable to and even better than those of the only FDA/WHO-approved anti-COVID-19 drug remdesivir along with its potent active metabolite GS-441524). The current research study supports the hypothesis that teriflunomide may inhibit SARS-CoV-2 replication in a triple mode of action through integrating the newly-discovered mechanism of nCoV-RdRp-inhibiting action with the previously-known two mechanisms of anticoronaviral-2 action. Additionally, teriflunomide attacks the inflammatory COVID-19 immune storm also in a triple mode of immunomodulatory action. Hopefully, the triple SARS-CoV-2 attacker (or the sextet COVID-19 attacker) teriflunomide can be further subjected to *in vitro/in vivo* anti-COVID-19 assays together with preclinical/clinical studies and trials in an attempt to assess and successfully confirm its comprehensive pharmacological bioactivities against SARS-CoV-2 to be efficiently used as an available choice in the COVID-19 therapy in the near future. In a word, teriflunomide is computationally and hypothetically proposed to be a potential effective anti-COVID-19 drug (i.e., a potent candidate anticoronaviral-2 agent), since it can potentially take integrative and comprehensive roles in the treatment of COVID-19 *via* its dual mode of six synergistic mechanisms of action (which are perfectly complementary to each other in COVID-19 therapy).

Declaration of competing interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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