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Salvia Officinalis and *Malva Sylvestris* Medicinal Plants as a Source of Potent Bioactive Compounds with Its Synergistic Antiviral Properties Against COVID-19: *in silico analysis*

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Abstract:

Salvia officinalis and *Malva sylvestris* can be used as a preventative treatment activity against the COVID-19 because the antiviral potential of *Salvia officinalis* and *Malva sylvestris* have secondary metabolites. We investigated the chemistry and biology of medicinal plants in terms of activity against the COVID-19 and described the potential of antiviral activity of *Salvia officinalis* and *Malva sylvestris* using the in-silico method. In this study, the Synergistic effect of selected plants; tiliroside in *Malva sylvestris* is more effective with the *Salvia officinalis* herb than the single components. In addition, 4-hydroxybenzoic acid and 9,12,13-trihydroxyoctadeca-10,15-dienoic acid were revealed that to be good candidates for synergistic effects, like tiliroside. The results of the current study indicate promising natural secondary metabolites as potential inhibitors of M^{pro}.

Worldwide, access to drugs used for treatment in COVID-19 infection and vaccines used for protection is under the control of states; unfortunately, it is necessary to reach accessible and economical products in the treatment of this disease to get rid of this pandemic as soon as possible. Here, we wanted to emphasize two separate biometabolites of plant origin, which we have found can be easily reached by humans and the antiviral effect can be much higher when used at the same time. Although the antiviral effects of these two bioactive compounds separately have been emphasized before; It is the first scientific study in the literature emphasizing that synergistic effects can occur when used at the same time.

Keywords: *Salvia officinalis*, *Malva sylvestris*, Phytotherapy, COVID-19, SARS-CoV-2

1. Introduction

COVID-19 is a quickly evolving epidemic and variable so drug improvement studies are clear to be a "requirement" against the COVID-19 but look out for in the investigation of new drug needs as the safety profile cannot be understood over a short period of time [1]. In such cases that lethal viral new disease, where no exact pharmacological drugs are in nowadays ready for prevention or treatment, a

lot of researchers are concentrated on bioactive compounds (secondary metabolites) of plants for prevention or treatment the COVID-19 from the using nature's power [2]. Currently in many areas of the world, due to lots of benefits of bioactive compounds (secondary metabolites) of medicinal plants on human metabolism against many diseases utilized as an immune booster and/or anti-infective agents [2]. In traditional and supplementary folk medicines, medicinal plants, spices, botanical detoxifiers [3], antioxidants [4], antiviral and anti-inflammatory effects [5] are used mediators' agents to prevent, treat, or minimize disease. For medicinal use, bioactive compounds (secondary metabolites) shouldn't be separated from each other, if the secondary metabolites separate, their prevention or treatment activity will be weaker or no activity according to the synergistic effect. Therefore, traditional, and supplementary folk medicines use secondary metabolites in medicinal plants [6]. According to the literature survey, Salvia officinalis and Malva sylvestris have antiviral activity against the COVID-19 [5, 7-9] so we focus on the synergistic effect of Salvia officinalis and Malva sylvestris as to whether the more powerful antiviral agent against the COVID-19. In phytotherapeutic studies using Salvia officinalis, was discovered that as little as 30 min of application was importantly diminished the COVID-19 replication in Vero-6 cells [10]. It was investigated how to use Salvia officinalis and Malva sylvestris and what role they have against COVID-19 [7].

In this study, we took advantage of the bioactive compounds (secondary metabolites) of plants which are nature's power, and used plants were Salvia officinalis (Sage) and Malva sylvestris (Mallow). For according to ethnobotanical use, the antiviral potential of Salvia officinalis and Malva sylvestris that have secondary metabolites was taken from the books in European Medicines Agency. We focus on this synergistic effect of Salvia officinalis and Malva sylvestris as the more powerful antiviral agent against the COVID-19. For this reason, firstly we determined the one-by-one effectivity to COVID-19 of some secondary metabolites then were evaluated the synergistic effect against the COVID-19. For the drug discovery approach to determine potential antiviral models, in silico works were applied.

2. Materials and Methods

Secondary metabolites of Salvia officinalis (sage) and Malva sylvestris (mallow) herbs which are α-thujone, β-thujone, camphor, 1,8-cineole, α-humulene, β-caryophyllene, viridiflorol for Salvia officinalis of sage; gallic acid, 4-hydroxybenzoic acid, 4-methoxybenzoic acid, linoleic acid, linolenic acid, 4-hydroxy-3-methoxybenzoic acid, dially-sulfide (EO), kaempferol, genistein, apigenin, myricetin, 4-hydroxycinnamic acid, ferulic acid, 2-hydroxydihydrocinnamate, quercetin, scopoletin, N-trans-feruloyl tyramine, α-sesquiterpene, 3-hydroxy-5,7-megastigmadien-9-one, stearic acid, 9,12,13-trihydroxyoctadeca-10,15-dienoic acid, tiliroside and Vitamin B6 for mallow herb are prepared using GaussView 6 [11]. These compounds were prepared using the "LigPrep" module of the Maestro 12.1 program [12-14]. In these calculations, method, and pH were selected as OPLS3e and 7.0±2.0, respectively. Original structures and possible states are taken into consideration for docking calculations. As for the protein selection, 6X6P [15], 6WTT [16], and 6YYT [17] were selected for spike glycoprotein (SG), main protease (MP), and RNA-dependent RNA polymerase (RdRp) of

SARS-CoV-2. These proteins are significant for this virus and have important roles in the survival of SARS-CoV-2. The mentioned proteins were prepared using the "ProteinPrep" module and pH was selected as 7.0±2.0, too. The receptor-binding domain (RBD) was defined for the molecular docking calculation using the "Receptor Grid Generation" module. For this purpose, x-y-z coordinates of RBD of 6X6P, 6WTT and 6YYT are 202.5-203.5-182.6, 0-25-(-15) and 85.4-90.7-101.2, respectively. Then, molecular docking calculations were performed using the "Ligand Docking" module. For the above analyses, Maestro 12.1 program was used. In addition to these calculations, the molecular mechanics energies combined with the Poisson–Boltzmann and surface area continuum solvation (MM-PBSA) calculations were done for selected ligand-protein interactions. The binding energies are calculated every 5 ns in the range of 0 – 100 ns. In these calculations, Nanoscale Molecular Dynamics (NAMD) [18] and Visual Molecular Dynamics (VMD) [19] software programs were used. The Gibbs binding energy was calculated using Equation (1).

$$\Delta G_{Binding} = G_{Complex}-(G_{Protein}+G_{Inhibitor}) \quad (1)$$

3. Results

3.1. Characterization

In SARS-CoV-2, there are three significant proteins, spike glycoproteins, main protease, and RNA-dependent RNA polymerase (RdRp). These proteins are represented in Figure 1. Main protease (M^{pro}) is significant for processing the polypeptides from viral DNA. Inhibition of this enzyme could inhibit viral replication. On the other hand, spike glycoprotein plays an important role in the virus entering the cell by binding to ACE2. Finally, RdRp regulates viral replication and is proposed as a potential therapeutic target to inhibit viral infection [7-9]. The protein structure of studied proteins is represented in Figure 1.

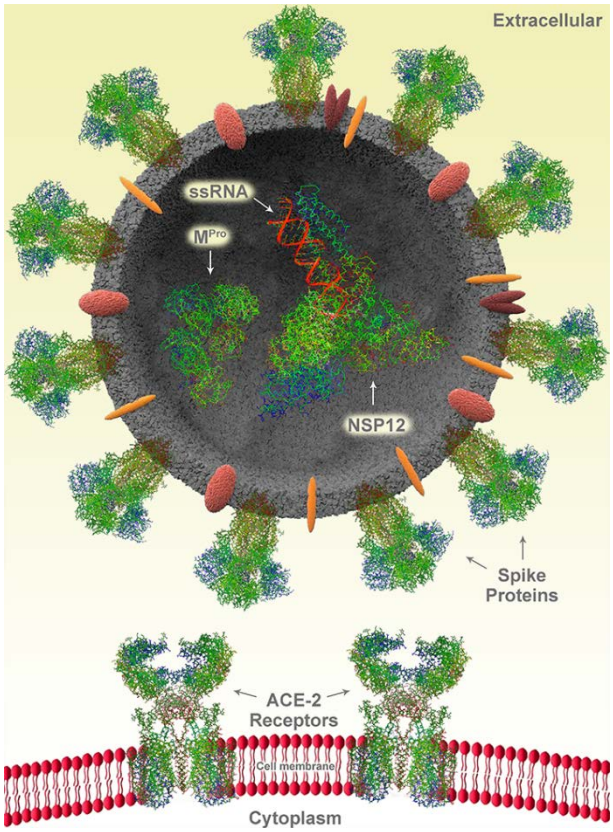

Figure 1. SARS-CoV-2 virus and its mechanism to enter the human cell.

3.2. The Interaction Between Active Ingredients of *Salvia Officinalis* of and Target Proteins

The active compounds which are α-thujone, β-thujone, camphor, 1,8-cineole, α-humulene, β-caryophyllene, viridiflorol are minimized at the OPLS3e method. Molecular docking calculations are performed, and their results are summarized in Table 1.

Table 1. Molecular docking results of *Salvia officinalis* herb against SARS-CoV-2.

Compound	**Docking Score**[a]	**LE**[a]	$\mathbf{E_{vdw}}$[a]	$\mathbf{E_{coul}}$[a]	$\mathbf{E_{interaction}}$[a]
For **6X6P**					
Viridiflorol	-5.374	-0.336	-16.906	-2.978	-19.884
β-Caryophyllene	-5.358	-0.357	-18.559	-0.121	-18.679
α-Thujone	-4.805	-0.437	-13.743	-1.894	-15.637
β-Thujone	-4.618	-0.420	-13.276	-2.420	-15.696
1,8-Cineole	-4.487	-0.408	-17.626	-2.164	-19.790
α-Humulene	-4.380	-0.292	-20.412	-0.177	-20.588
Camphor	-4.145	-0.377	-16.106	-2.172	-18.278
For **6WTT**					
α-Thujone	-5.347	-0.486	-17.334	-1.558	-18.892
β-Thujone	-5.080	-0.462	-14.863	-3.239	-18.102
Camphor	-4.938	-0.449	-19.080	-1.706	-20.786
α-Humulene	-4.255	-0.284	-18.977	-0.044	-19.021
For **6YYT**					
Viridiflorol	-5.932	-0.371	-19.635	-4.118	-23.753
1,8-Cineole	-5.652	-0.514	-26.395	-0.642	-27.036
β-Thujone	-5.602	-0.509	-18.383	-2.395	-20.778
Camphor	-5.491	-0.499	-22.655	-1.404	-24.059
α-Humulene	-5.414	-0.361	-20.941	-0.294	-21.235
α-Thujone	-5.280	-0.480	-19.772	-2.164	-21.936
β-Caryophyllene	-4.671	-0.311	-12.671	0.219	-12.453

[a]in kcal/mol

LE is ligand efficiency.

According to Table 1, some ingredients are active against the SARS-CoV-2. However, better results are obtained against RdRp of SARS-CoV-2. Because docking score is generally lower than -5.000 kcal/mol. In addition to these results, interaction energies are better in RdRp than those of others. On the other hand, this herb seems as active against the SG protein of SARS-CoV-2 while it is not as effective for the main protease as other proteins. The docking structure in 6YYT of the best two ingredients which are viridiflorol and 1,8-cineole is represented in Figure 2. Additionally, these compounds are found as effective for SG protein.

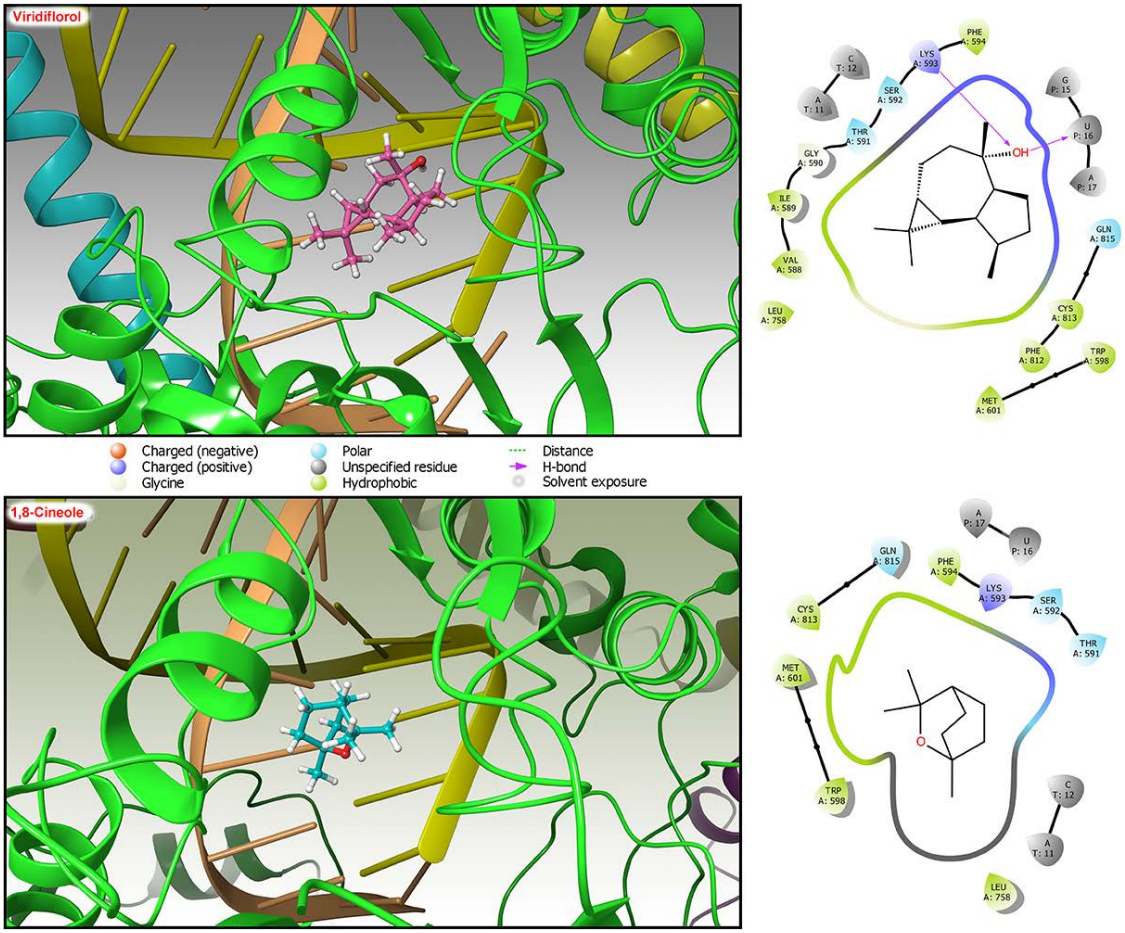

Figure 2. Molecular docking and interactions of viridiflorol and 1,8-cineole components *Salvia officinalis*.

3.3. The Interaction Between Malva sylvestris and Target Proteins

The active components in *Malva sylvestris* herb are gallic acid, 4-hydroxybenzoic acid, 4-methoxybenzoic acid, linoleic acid, linolenic acid, 4-hydroxy-3-methoxybenzoic acid, dially-sulfid (EO), kaempferol, genistein, apigenin, myricetin, 4-hydroxycinnamic acid, ferulic acid, 2-hydroxydihydrocinnamate, quercetin, scopoletin, *N*-trans-feruloyl tyramine, α-sesquiterpene, 3-hydroxy-5,7-megastigmadien-9-one, stearic acid, 9,12,13-trihydroxyoctadeca-10,15-dienoic acid, tiliroside, and Vitamin B6. These molecules are minimized using the OPLS3e method in Maestro 12.1 software. The related calculations are performed and docking results are given in Table 2.

Table 2. Molecular docking results of *Malva sylvestris* herb against SARS-CoV-2.

Compound	**Docking Score**[a]	**LE**[a]	**E_{vdw}**[a]	**E_{coul}**[a]	**$E_{interaction}$**[a]
For **6X6P**					
Tiliroside	-8.271	-0.192	-47.034	-13.607	-60.641
Apigenin	-6.595	-0.330	-25.547	-8.750	-34.297
Genistein	-6.170	-0.309	-27.524	-5.603	-33.128
N-Trans-feruloyl tyramine	-6.044	-0.263	-30.567	-12.249	-42.816
Quercetin	-5.819	-0.264	-28.476	-7.782	-36.258
Myricetin	-5.782	-0.251	-29.409	-8.831	-38.240
4-Hydroxybenzoic acid	-5.423	-0.542	-11.263	-13.031	-24.293
α-Sesquiterpene	-5.259	-0.292	-19.193	-4.368	-23.562
9,12,13-Trihydroxyoctadeca-10,15-dienoic acid	-5.002	-0.217	-29.642	-12.426	-42.068
Kaempferol	-4.832	-0.230	-21.852	-11.650	-33.502
Vitamin B6	-4.774	-0.398	-14.104	-10.542	-24.646
Scopoletin	-4.750	-0.339	-18.876	-4.624	-23.500
4-Hydroxy-3-methoxybenzoic acid	-4.674	-0.390	-14.320	-11.093	-25.413
Gallic acid	-4.531	-0.378	-16.887	-8.400	-25.287
Ferulic Acid	-4.321	-0.309	-15.386	-12.875	-28.261
4-Methoxybenzoic acid	-4.273	-0.388	-15.733	-4.962	-20.695
4-Hydroxycinnamic acid	-4.170	-0.347	-15.555	-10.045	-25.601
2-Hydroxy dihydrocinnamate	-3.608	-0.301	-15.720	-9.545	-25.265
Linoleic acid	-2.447	-0.122	-19.766	-18.958	-38.724

Linolenic acid	-1.883	-0.094	-19.119	-19.061	-38.180
Stearic acid	-0.450	-0.023	-24.489	-11.854	-36.342
For **6WTT**					
Genistein	-7.418	-0.371	-34.896	-5.186	-40.081
Tiliroside	-6.860	-0.160	-44.844	-10.893	-55.737
Myricetin	-6.854	-0.298	-33.782	-10.042	-43.824
Kaempferol	-6.796	-0.324	-33.357	-4.529	-37.886
Apigenin	-6.611	-0.331	-32.439	-3.396	-35.835
Quercetin	-6.419	-0.292	-34.022	-4.419	-38.441
Scopoletin	-5.955	-0.425	-21.513	-4.534	-26.047
9,12,13-trihydroxyoctadeca-10,15-dienoic acid	-5.890	-0.256	-27.450	-18.460	-45.910
N-Trans-feruloyl tyramine	-5.833	-0.254	-34.276	-6.479	-40.756
Gallic acid	-5.368	-0.447	-13.576	-13.858	-27.435
Ferulic Acid	-5.178	-0.370	-19.843	-8.126	-27.969
4-Hydroxy-3-methoxybenzoic acid	-5.019	-0.418	-19.010	-6.199	-25.210
4-Hydroxycinnamic acid	-4.837	-0.403	-18.049	-9.953	-28.002
4-Methoxybenzoic acid	-4.727	-0.430	-17.593	-6.887	-24.481
Vitamin B6	-4.520	-0.377	-15.772	-8.954	-24.726
4-Hydroxybenzoic acid	-4.495	-0.449	-16.372	-7.182	-23.554
2-Hydroxy dihydrocinnamate	-4.087	-0.341	-18.862	-9.177	-28.039
Linolenic acid	-1.434	-0.072	-32.346	-7.084	-39.431
Linoleic acid	-0.606	-0.030	-29.885	-6.215	-36.100
Stearic acid	0.544	0.027	-21.800	-9.714	-31.514
For **6YYT**					

Quercetin	-9.274	-0.422	-34.840	-19.441	-54.281
Vitamin B6	-7.363	-0.614	-14.512	-25.101	-39.613
N-Trans-feruloyl tyramine	-7.244	-0.315	-26.152	-15.816	-41.968
Scopoletin	-6.619	-0.473	-29.302	-8.966	-38.267
9,12,13-Trihydroxyoctadeca-10,15-dienoic acid	-6.417	-0.279	-34.522	-15.894	-50.416
2-Hydroxy dihydrocinnamate	-6.043	-0.504	-22.480	-14.768	-37.248
α-Sesquiterpene	-5.955	-0.331	-28.322	-4.685	-33.008

[a]in kcal/mol

LE is ligand efficiency.

According to Table 2, *Malva sylvestris* can be effective in the treatment of COVID-19. Especially, the main protease is mainly inhibited by this herb. However, the best docking score is obtained in the inhibiting of RdRp which is -9.274 kcal/mol. As a result, it is predicted that the *Malva sylvestris* herb may be effective in the treatment of COVID-19 in terms of phytotherapy. Molecular docking structures between tiliroside and 6X6P; quercetin and 6YYT are represented in Figure 3.

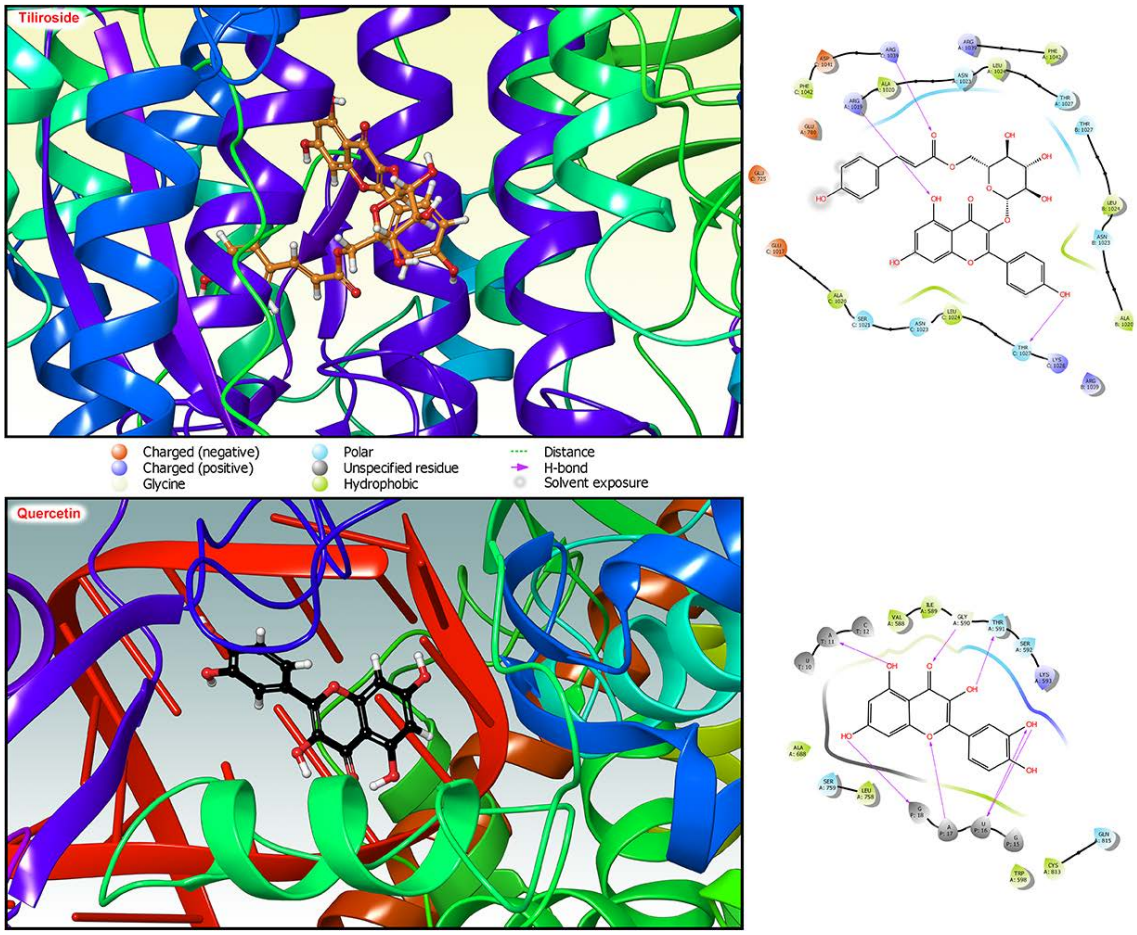

Figure 3. Molecular docking and interactions of tiliroside and quercetin components from *Malva sylvestris*.

3.4. Investigations of Synergistic Effect

Studied herbs seem as active against the SARS-CoV-2 concerning the above results. Especially RNA-dependent RNA polymerase can be inhibited by them. In this section, a synergistic effect is examined in detail for RdRp protein. For this purpose, these two herbs are considered for the docking calculations. Molecular docking results belonging to RdRp are given in Table 3.

Table 3. Molecular docking results of *Salvia officinalis* and *Malva sylvestris* herbs.

Compound	**Docking Score**[a]	**LE**[a]	**E_{vdw}**[a]	**E_{coul}**[a]	**$E_{interaction}$**[a]
For **6YYT** with α-thujone					
Tiliroside	-5.602	-0.509	-18.383	-2.395	-20.778
4-Hydroxybenzoic acid	-5.602	-0.509	-18.383	-2.395	-20.778
With Camphor					

Tiliroside	-5.491	-0.499	-22.655	-1.404	-24.059
9,12,13-Trihydroxyoctadeca-10,15-dienoic acid	-5.491	-0.499	-22.655	-1.404	-24.059
With 1,8-cineole					
Tiliroside	-5.652	-0.514	-26.395	-0.642	-27.036
With α-humulene					
Tiliroside	-5.414	-0.361	-20.941	-0.294	-21.235
4-Hydroxybenzoic acid	-5.414	-0.361	-20.941	-0.294	-21.235
9,12,13-Trihydroxyoctadeca-10,15-dienoic acid	-5.414	-0.361	-20.941	-0.294	-21.235
With β-caryophyllene					
4-Hydroxy-3-methoxybenzoic acid	-4.671	-0.311	-12.671	0.219	-12.453
4-Hydroxybenzoic acid	-4.671	-0.311	-12.671	0.219	-12.453
Vitamin B6	-4.671	-0.311	-12.671	0.219	-12.453
Tiliroside	-4.671	-0.311	-12.671	0.219	-12.453
Gallic acid	-4.671	-0.311	-12.671	0.219	-12.453
With Viridiflorol					
Tiliroside	-5.932	-0.371	-19.635	-4.118	-23.753
9,12,13-Trihydroxyoctadeca-10,15-dienoic acid	-5.932	-0.371	-19.635	-4.118	-23.753

[a]in kcal/mol

LE is ligand efficiency.

According to Table 3, there is a synergistic effect. Especially, tiliroside in Malva sylvestris is so effective with the Salvia officinalis herb. Because it is pretty much inhibited the RdRp of SARS-CoV-2 with Salvia officinalis. It can be said that there is a good synergistic effect. In addition to these results, 4-hydroxybenzoic acid and 9,12,13-trihydroxyoctadeca-10,15-dienoic acid were found to be good candidates for synergistic effect, if not as much as tiliroside. As a result, Salvia officinalis and Malva sylvestris can be used separately against SARS-CoV-2, but if these herbs are used together, it is seen that there could be an almost two-fold antiviral effect.

3.5. MM-PBSA Calculations

The molecular mechanics energies combined with the Poisson–Boltzmann and surface area continuum solvation (MM/PBSA) calculation is significant to determine the interaction stability between ligand and protein. The MM/PBSA calculations were performed for 6YYT-viridiflorol and 6YYT-genistein because the best protection is obtained for 6YYT. The *Malva sylvestris* and *Salvia officinalis* herb is effective against COVID-19. The binding energy is calculated for the range of 0 – 100 ns. The binding energies in every 5 ns with standard deviation are given in Table 4. Additionally, the energy distribution graph is plotted and represented in Figure 4.

Table 4. The binding energy in every 5 ns.

Time	6YYT-viridiflorol[a]	Standard Deviation[a]	6YYT-genistein[a]	Standard Deviation[a]
0	-939837.3	-	-958242.3	-
5	-762755.9	±46507.3	-773321.8	±48293.0
10	-748833.9	±3859.1	-759229.0	±3783.4
15	-749149.0	±312.4	-757647.5	±595.3
20	-748956.3	±524.5	-758896.6	±624.3
25	-749483.9	±601.0	-758659.6	±559.5
30	-747899.4	±535.5	-757689.1	±531.1
35	-748634.8	±535.0	-757597.1	±457.9
40	-748142.8	±453.4	-756958.8	±552.4
45	-748889.2	±799.1	-759652.2	±904.5
50	-747733.6	±455.8	-757807.2	±551.6
55	-749018.4	±544.8	-759029.3	±692.9
60	-748034.7	±816.2	-758572.1	±437.0
65	-746839.5	±715.1	-758355.0	±461.1
70	-748608.7	±549.3	-759660.1	±668.2
75	-747726.3	±614.8	-758691.3	±738.1
80	-747927.2	±534.9	-757259.8	±1038.6
85	-748970.9	±554.0	-757129.7	±422.8

90	-747714.8	±405.0	-758366.3	±795.3
95	-747747.4	±440.5	-758835.9	±465.5
100	-747183.6	±535.2	-757099.9	±550.5

[a]in kcal/mol

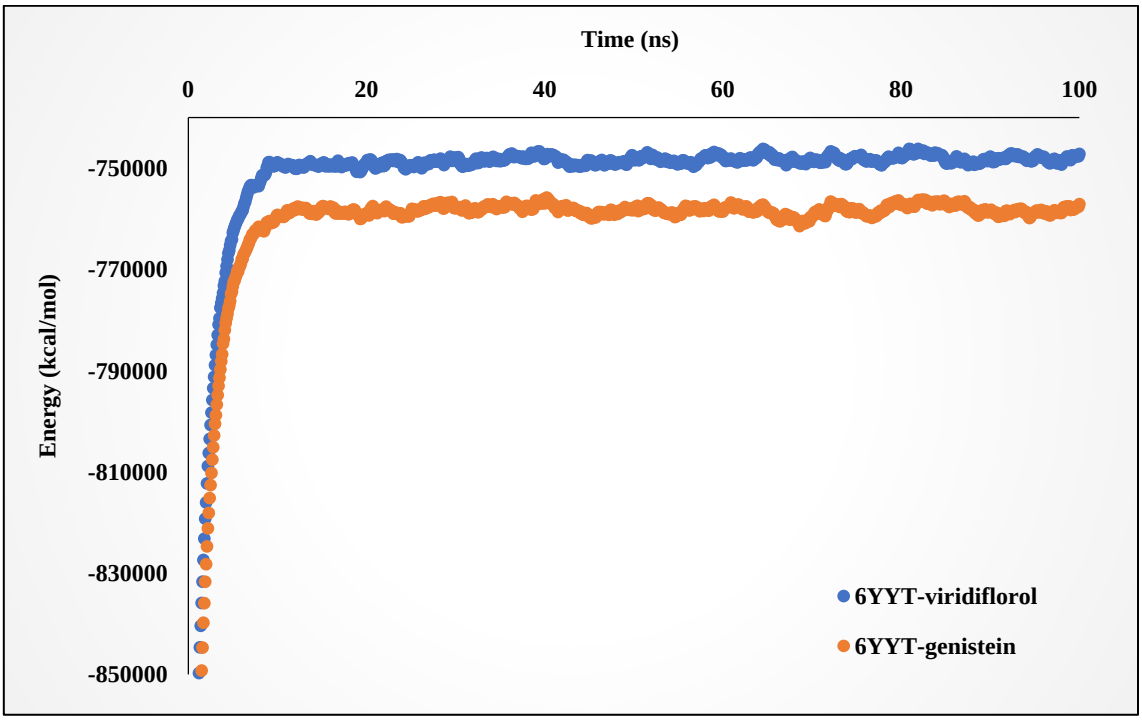

Figure 4. The binding energy distribution of 6YYT-viridiflorol and 6YYT-genistein interactions.

According to Figure 4 and Table 4, the binding energies are negative, and it implies that there are good interactions. The interaction between genistein and 6YYT is better than the other. However, it can be said that each interaction is found as good. So, *Malva sylvestris* and *Salvia officinalis* herbs are effective in inhibiting of RdRp of SARS-CoV-2.

In our literature review, we found scientific studies emphasizing the possible antiviral effects of *Malva sylvestris* and *Salvia Officinalis* on COVID-19 or that they can be used in adjuvant symptomatic treatment [20-23]. Unlike scientific studies in the literature, it is the first scientific article emphasizing that both ingredients have a synergistic effect and more antiviral effects on COVID-19. We think that comprehensive studies on this subject should be conducted on humans and animals, and its effects on possible therapeutic use, the effects of use dose on oral or inhaler therapy, locally or systemically on the infection of the COVID-19 virus should be investigated. In the light of the information, we have emphasized here, it is not only for oral-systemic use; We think that it can be used nasally or orally in the form of steam application in all individuals with COVID-19 infection, symptomatic or asymptomatic, and in this way, it can reduce the destruction of the olfactory area or

other nerve damage in the COVID-19 infected patients with a synergistic effect. Since the drugs and vaccines normally used in the treatment of COVID-19 are provided only under the control of the ministries of health in the relevant countries and certain countries have these opportunities, we wanted to emphasize the synergistic antiviral effect of these two separate herbal ingredients available worldwide.

4. Conclusion

The COVID-19 pandemic has had a catastrophic impact on human health and global economies. SARS-CoV-2 main protease (Mpro) may well prove to be the Achilles heel of viral replication. The COVID-19 pandemic has had a disastrous effect on human health, industrial economies such as manufacturing, trade, finance, and politics, etc. all over the world countries. So, we focus on the likelihood of the natural secondary metabolites in some medicinal and aromatic plants in way of the user as a potential drug. In this study, we used Salvia officinalis and Malva sylvestris plants as a potential secondary metabolites source against the spike glycoprotein (6X6P), main protease (6WTT), and RNA-dependent RNA polymerase (6YYT) that is the protein of the COVID-19. Molecular docking calculation using the “Receptor Grid Generation” module was used for calculating the RBD values. The “Ligand Docking” module was applied to determine the molecular docking calculations of selected secondary metabolites. Molecular docking calculations revealed the high interaction energies of viridiflorol and 1,8-cineole can be effected to SG protein in terms of Salvia officinalis (according to docking scores in Table 1). In experimental studies with tiliroside and quercetin which are located in Malva sylvestris inhibited 6X6P and 6YYT, respectively. According to evaluating the synergistic effect of selected plants; tiliroside in Malva sylvestris is more effective with the Salvia officinalis herb than the single state. In addition, 4-hydroxybenzoic acid and 9,12,13-trihydroxyoctadeca-10,15-dienoic acid were revealed that to be good candidates for synergistic effect, if not as much as tiliroside.

The results of the current study reveal promising natural secondary metabolites as potential inhibitors of Mpro. Due to the restriction of experimental tests, anymore in vitro and/or in vivo exploration of the potent natural secondary metabolites under study is highly suggested as a promising starting point for the development of natural drugs targeting SARS-CoV-2 Mpro.

At the same time, we wanted to investigate the synergistic effects of the metabolites obtained from these two separate aromatic plants, which can be used by people, are easy to use, economically available to all patients, preventive, and can be used as an aid in treatment.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

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Abbreviations

M^{pro}, Main protease; COVID-19, Coronavirus disease 2019; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SG, Spike glycoprotein; MP, Main protease; RdRp, RNA dependent RNA polymerase; MM-PBSA, Molecular mechanics-Poisson Boltzmann surface area; NAMD, Nanoscale Molecular Dynamics; VMD, Visual Molecular Dynamics; ns, Nanosecond; ACE2, Angiotensin-converting enzyme-2; PDB, Protein data bank.

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