(*R*)- (+)-Rosmarinic Acid as an Inhibitor of Herpes and Dengue Viruses Replication: An *In-silico* Assessment

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Table. S1. Site scores and volumes of viral protein binding sites.

S. No.	Target Code	Score	Volume	Active residues of Site within 3Å
1.	1F5Q	1.015	287.777	LYS89, ASP86, GLN85, HIE84, LEU83, PHE82, GLU81, PHE80, LEU143, ALA144, ASP145, PHE146, GLY147, GLU51, LYS33, LEU32, ALA31, LEU134, GLN131, VAL64, ILE64 and LEU55
2.	2J7W	1.049	493.92	PRO319, THR317, PRO258, ASN207, ARG257, LYS211, ALA213, ASP276, PHE277 and ASP278
3.	4OIG	1.032	364.251	ARG481, VAL450, THR571, LYS575, VAL577, VAL579, VAL358, LYS355, PHE354, TYR299, TRP302, ILE592, GLN602, SER600 and GLY599

Table. S2. Binding affinities among the residues of viral proteins and (*R*)- (+)-rosmarinic acid

Docked complex	Residues contribution for interactions	Interactions	
		Back bone with H-bond distances	Other contacts
1F5Q with RA	PHE146, GLU51 (Covalent binding), LYS33, PHE80, LEU83 & HIE84	PHE146 (2.14), GLU51 (1.47 & 2.06), LYS33 (1.70), LEU83 (2.13) & HIE84 (2.14)	PHE80 (π-π)
2J7W with RA	THR571, VAL450, PHE354 & SER600	THR571 (2.28), VAL450 (2.10), PHE354 (1.71) & SER600 (2.54)	-
4OIG with RA	THR317 (Covalent binding), ARG257, LYS211, PHE277 & ASP278	THR317 (1.96 & 1.92), ARG257 (1.94), PHE277 (2.76) & ASP278 (1.92)	LYS211 (Salt bridge & π-cation) and ARG257 (Salt bridge)

Table. S3. The biomedical drug probabilities of (*R*)- (+)-rosmarinic acid by triggering or inhibiting the enzymes in human body (Predicted by Pass server)

Biological activities	Pa (probability to be active)	Pi (probability to be inactive)
Membrane integrity agonist	0.956	0.003
Feruloyl esterase inhibitor	0.938	0.003
Antihypoxic	0.921	0.002
Monophenol monooxygenase inhibitor	0.836	0.003
Antidiabetic	0.799	0.005
CYP2J substrate	0.804	0.020
GST A substrate	0.787	0.011
Reductant	0.779	0.004
Membrane permeability inhibitor	0.785	0.012
Pyruvate decarboxylase inhibitor	0.766	0.004
Preneoplastic conditions treatment	0.763	0.005
Chlordecone reductase inhibitor	0.780	0.024
Mucomembranous protector	0.779	0.024
Linoleate diol synthase inhibitor	0.757	0.008
APOA1 expression enhancer	0.751	0.004
Free radical scavenger	0.745	0.003
TNF expression inhibitor	0.744	0.005
4-Hydroxybenzoate 3-monooxygenase inhibitor	0.735	0.002
JAK2 expression inhibitor	0.745	0.013
MMP9 expression inhibitor	0.730	0.005
Anti-mutagenic	0.722	0.005
Lipid peroxidase inhibitor	0.719	0.005
Mucositis treatment	0.725	0.021
Ubiquinol-cytochrome-c reductase inhibitor	0.752	0.049
4-Coumarate-CoA ligase inhibitor	0.705	0.003
Gluconate 2-dehydrogenase (acceptor) inhibitor	0.710	0.051
Membrane integrity agonist	0.956	0.003
Feruloyl esterase inhibitor	0.938	0.003
Antihypoxic	0.921	0.002
Monophenol monooxygenase inhibitor	0.836	0.003
Antidiabetic	0.799	0.005
CYP2J substrate	0.804	0.020

Table. S4. Adverse effect of Aciclovir predicted by Pass Server

Adverse Effects	Pa (probability to be active)	Pi (probability to be inactive)

Pure red cell aplasia	0.986	0.001
Coma	0.986	0.003
Ataxia	0.974	0.004
Acidosis	0.973	0.003
Dysarthria	0.968	0.002
Splenomegaly	0.934	0.001
Myoclonus	0.933	0.003
Anemia	0.931	0.005
Consciousness alteration	0.929	0.006
Hyperthermic	0.926	0.004
Hepatitis	0.927	0.005
Diarrhea	0.926	0.008
Tremor	0.921	0.005
Thrombocytopenia	0.909	0.005
Stomatitis	0.910	0.009
Xerostomia	0.905	0.008
Leukopenia	0.901	0.005
Tachycardiac	0.902	0.006
Headache	0.902	0.008
Drowsiness	0.892	0.010
Paralysis	0.885	0.005
Depression	0.873	0.005
Dizziness	0.879	0.011
Sensory disturbance	0.873	0.012
Emetic	0.871	0.011
Hematotoxic	0.874	0.015
Pain	0.867	0.010
Agranulocytosis	0.864	0.008
Dermatitis	0.865	0.012
Sweating	0.856	0.010
Nausea	0.854	0.015
Nephrotoxic	0.838	0.008
Excitability	0.839	0.011
Dyskinesia	0.838	0.011
Toxic. gastrointestinal	0.844	0.019
Sleep disturbance	0.841	0.018
Thrombophlebitis	0.830	0.007
Conjunctivitis	0.837	0.018
Neurotoxic	0.811	0.016
Hypertensive	0.802	0.015
Gastrointestinal disturbance	0.779	0.008
Ocular toxicity	0.784	0.024
Inflammation	0.761	0.019
Reproductive dysfunction	0.764	0.024
Bronchoconstrictor	0.749	0.011
Hepatotoxic	0.758	0.026
Allergic contact dermatitis	0.721	0.017
Glaucoma	0.702	0.005
Behavioral disturbance	0.716	0.037

Table. S5. Adverse effect of Famiciclovir predicted by Pass Server

Adverse Effects	**Pa (probability to be active)**	**Pi (probability to be inactive)**

Pure red cell aplasia	0.824	0.019
Splenomegaly	0.767	0.010

Table. S6. Adverse effect of Famiciclovir predicted by Pass Server

Adverse Effects	**Pa (probability to be active)**	**Pi (probability to be inactive)**
Coma	0.940	0.004
Headache	0.926	0.006
Pure red cell aplasia	0.919	0.004
Myoclonus	0.911	0.003
Dizziness	0.914	0.008
Thrombocytopenia	0.908	0.005
Drowsiness	0.910	0.009
Leukopenia	0.904	0.005
Splenomegaly	0.898	0.002
Agranulocytosis	0.894	0.005
Pain	0.897	0.008
Sensory disturbance	0.893	0.010
Dermatitis	0.884	0.009
Nausea	0.885	0.011
Sleep disturbance	0.878	0.014
Hematotoxic	0.867	0.016
Excitability	0.858	0.009
Xerostomia	0.858	0.011
Ataxia	0.854	0.008
Emetic	0.859	0.013
Toxic. gastrointestinal	0.850	0.018
Sweating	0.837	0.013
Nephrotoxic	0.812	0.011
Consciousness alteration	0.810	0.015
Dysarthria	0.784	0.008
Behavioral disturbance	0.795	0.025
Stomatitis	0.777	0.020
Tremor	0.759	0.015
Acidosis	0.753	0.023
Depression	0.727	0.014
Delirium	0.728	0.018
Thrombophlebitis	0.702	0.020
Diarrhea	0.716	0.036

Table. S7. Adverse effect of Valaciclovir predicted by Pass Server

Adverse Effects	**Pa (probability to be active)**	**Pi (probability to be inactive)**

Coma	0.986	0.003
Pure red cell aplasia	0.982	0.001
Ataxia	0.976	0.004
Toxic. respiration	0.977	0.005
Splenomegaly	0.964	0.001
Delirium	0.955	0.003
Myoclonus	0.950	0.002
Tremor	0.951	0.004
Hepatitis	0.949	0.004
Consciousness alteration	0.938	0.005
Thrombocytopenia	0.926	0.005
Acidosis	0.924	0.007
Leukopenia	0.911	0.005
Drowsiness	0.913	0.008
Headache	0.910	0.007
Stomatitis	0.911	0.009
Dysarthria	0.904	0.003
Agranulocytosis	0.898	0.004
Dizziness	0.895	0.010
Emetic	0.891	0.009
Sweating	0.887	0.007
Sensory disturbance	0.889	0.010
Necrosis	0.886	0.008
Anemia	0.881	0.008
Nausea	0.881	0.011
Gastrointestinal disturbance	0.873	0.005
Allergic dermatitis	0.869	0.004
Hematotoxic	0.873	0.015
Dermatitis	0.869	0.012
Dyskinesia	0.859	0.010
Toxic. gastrointestinal	0.863	0.016
Nephrotoxic	0.854	0.007
Neurotoxic	0.856	0.011
Inflammation	0.851	0.010
Tachycardiac	0.830	0.013
Hypotension	0.819	0.013
Xerostomia	0.806	0.016
Thrombophlebitis	0.798	0.009
Diarrhea	0.802	0.025
Ocular toxicity	0.799	0.022
Hypertensive	0.792	0.016
Behavioral disturbance	0.788	0.026
Hyperthermic	0.772	0.011
Hepatotoxic	0.772	0.024
Excitability	0.738	0.024
Conjunctivitis	0.742	0.029
Glaucoma	0.709	0.005
Paralysis	0.706	0.018
Bronchoconstrictor	0.703	0.017

Table. S8. Adverse effect of (*R*)-(+)-rosmarinic acid predicted by Pass Server

Adverse Effects	**Pa (probability to be active)**	**Pi (probability to be inactive)**
Hematemesis	0.797	0.014
Urine discoloration	0.739	0.015
Shivering	0.748	0.059
Ulcer, aphthous	0.707	0.041

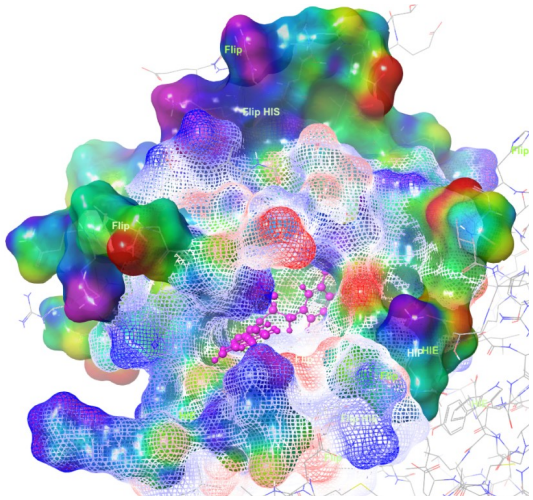

Fig. S1. Binding Site of (*R*)-(+)-rosmarinic acid in 1F5Q

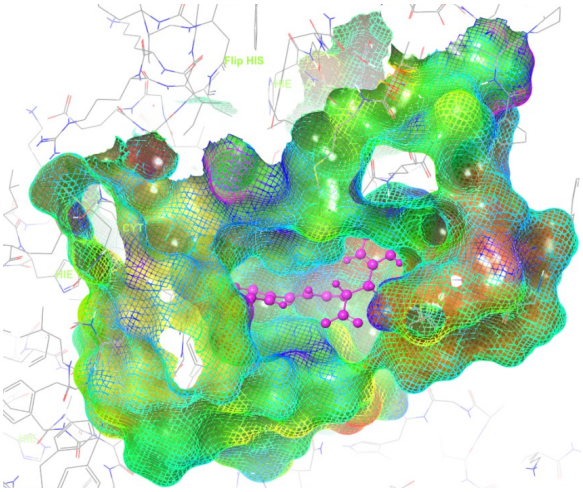

Fig. S2. Binding Site of (*R*)-(+)-rosmarinic acid in 2J7W

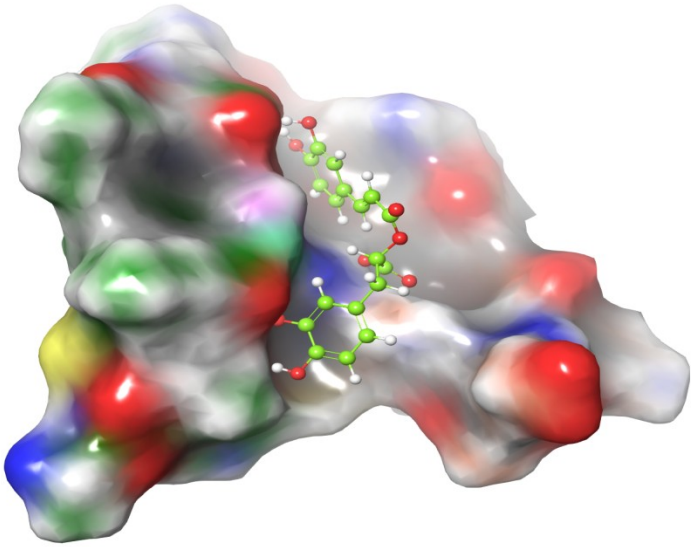

Fig. S3. Binding Site of (*R*)-(+)-rosmarinic acid in 4OIG

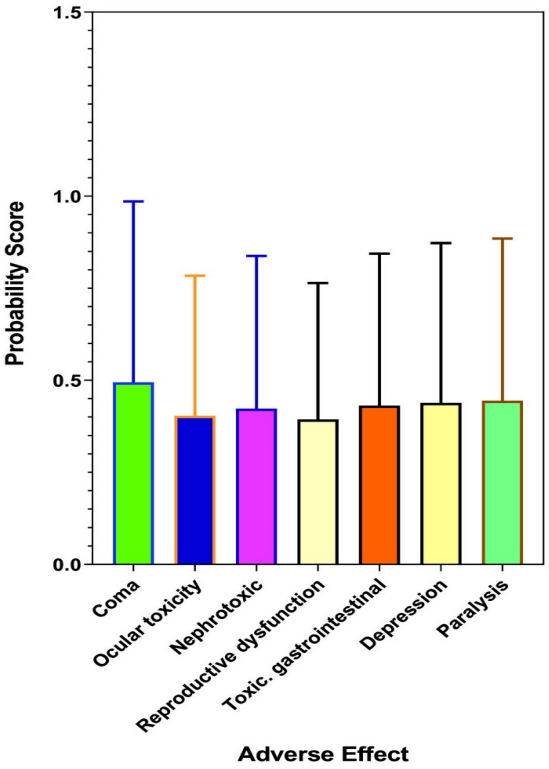

Fig. S4. Probability scores reflect the most notable adverse effect of the acyclovir in the human health (Predicted by Pass Server)

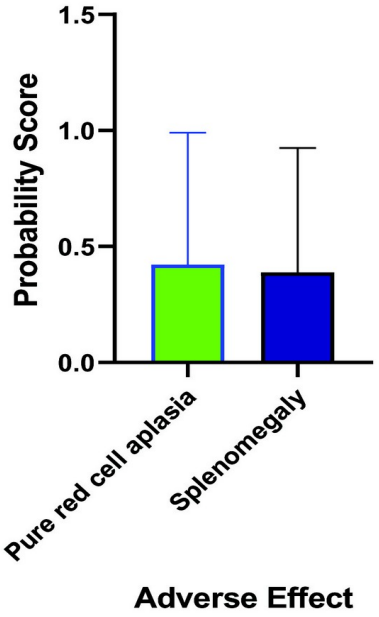

Fig. S5 Probability scores reflect the most notable adverse effect of the Famiciclovir in the human health (Predicted by Pass Server)

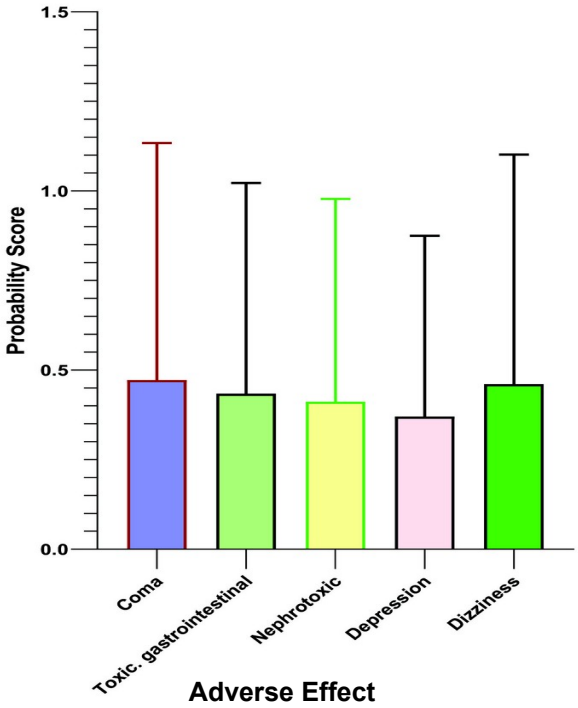

Fig. S6 Probability scores reflect the most notable adverse effect of the Penciclovir in the human health (Predicted by Pass Server)