**Supplementary Table 1 (ST1). Binding energies of WS phytoconstituents with unbound Spike receptor-binding domain (RBD) of SARS-CoV-2 (PDB ID: 6M0J) in comparison to the FDA approved standard reference drugs (Arbidol and Losartan)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **AutoDock v4.2.6** | | | **AutoDock vina** | | | **iGEMDOCK v2.1** | | | | | |
| **S.No** | **Ligands** | **BE (kcal/mol)** | **Kd** | **Interacting amino acids** | **BE**  **(kcal/mol)** | **Kd** | **Interacting amino acids** | **T.E.**  **(kcal/mol)** | **VDW** | **HB** | **EI** | **Interacting amino acids** |
| **1.** | Withaferin A | -4.19 | 852.71 µM | Arg466, Asn354, Arg355, Lys356, Val341, Ala344, Glu340 | -8.9 | 290.34 nM | *Phe374, Ser373, Val367,* Asp364, Phe338, Val362, Ala363, *Cys336,Leu335, Leu368, Asn343, Phe342, Ser371* | -92.24 | -77.43 | -14.81 | 0 | Arg364, *Leu335, Cys336, Val367, Leu368,Ser371, Phe374, Ser373,* Trp436, *Asn343, Phe342,* Gly339 |
| **2.** | Withanolide A | -3.68 | 1.99 mM | Arg466, Phe464, Ala352, Trp353, Asn354, Arg355 | -8.2 | 900.88 nM | *Leu441, Phe374,* Leu368, Phe342, *Trp436, Asn343,* Val367, Phe338, Gly339, *Asn440, Ser373, Ser371* | -85.08 | -73.05 | -12.03 | 0 | *Ser371, Ser373,* Phe374, Ser375, *Trp436,* Asn437, *Asn440,Leu441, Phe342, Asn343* |
| **3.** | Withanolide B | -2.97 | 6.7 mM | Arg466, Arg355, Asn354, Lys356, Arg357 | -8.3 | 780.68 nM | Asn440, Trp436, Ser371, Phe342, Val367, Phe338, Leu368, Gly339, Asn343, Phe374, Ser373, Leu441 | -89.86 | -69.06 | -20.79 | 0 | Phe456, Arg454, Arg457, Lys458, Ser459, Lys462, Glu465, Asp467, Ser469, Glu471, Pro491, Tyr473, |
| **4.** | Withanolide D | -4.55 | 465.0 µM | Phe464, Arg466, Arg355, Asn354, Trp353 | -8.3 | 783.68 nM | *Phe374, Ser373, Val367,* Asp364, *Phe338,* Val362, Ala363, *Cys336, Leu335, Leu368, Asn343, Phe342, Ser371* | -85.28 | -73.28 | -11.99 | 0 | *Asn343, Phe342,* Gly339, *Phe338,* *Cys336, Leu335, Val367, Leu368, Ser371, Phe374, Ser373* |
| **5.** | Withanolide E | -5.14 | 171.94 µM | *Phe464, Arg466,* Ile468, Ala352, *Trp353,* Asn354, *Arg355* | -8.2 | 903.88 nM | Tyr505, Gln493, Leu455, Phe456, Tyr453, Tyr495, Arg403, Phe497, Gly496, Asn501 | -88.38 | -68.66 | -19.73 | 0 | Lys462, Pro463, Glu465, *Arg466, Phe464, Trp353, Arg355* |
| **6.** | Withanone | -2.77 | 9.4 mM | Phe464, Arg466, Arg355, Asn354, Trp353 | -8.6 | 448.56 nM | Trp436, Phe342, Asn343, Phe338, Phe374, Cys336, Gly339, Leu335, Ser373, Leu368, Val367, Ser371 | -93.84 | -74.78 | -19.06 | 0 | Tyr453, Gln493, Ser494, Tyr495, Gly496, Arg403, Tyr505, Gly502, Asn501, Gln498, Thr500 |
| **7.** | Viscosalactone B | -4.35 | 647.61 µM | *Arg466, Arg355,* Asn354, Lys356, Val341, Glu340, Ala344 | -8.4 | 707.34 nM | Glu465, *Arg466, Arg355,* Tyr396, Ser514, Phe515, Glu516, Thr430, Lys462, Pro463, Phe464, Pro426 | -87.54 | -85.59 | -1.94 | 0 | Trp436, Phe374, Ser373, Ser371, Leu368, Val367, Leu335, Cys336, Gly339, Phe338, Asn343, Phe342 |
| **8.** | Anaferine | -4.25 | 765.99 µM | Asn354, Ala348, Ser399, Phe347, Arg346, Val341, Ala344, Glu340, Lys356 | -5.5 | 91.44 µM | Phe374, Ser373, Val367, Trp436, Phe342, Asn343, Ser371, Leu368, Gly339, Phe338 | -71.43 | -67.13 | -4.30 | 0 | Lys458, Ser459, Tyr473, Arg457, Glu471, Asp467, Pro491, Phe456, Arg454 |
| **9.** | Withasomnine | -4.87 | 270.55 µM | Lys356, Asn354, Ala348, Ser399, Phe347, Val341, Arg346, Glu340, Ala344 | -6.1 | 30.85 µM | Leu335, Ser371, Leu368, Cys336, Phe374, Val367, Phe342, Gly339, Phe338 | -73.76 | -63.91 | -9.85 | 0 | Lys458, Ser459, Arg457, Phe456, Pro491, Ser469, Glu471, Arg454 |
| **10.** | Arbidol | -1.18 | 136.89 mM | Ile468, Arg466, Ala352, Trp353, Asn354, Arg355, Lys356 | -5.9 | 45.22 µM | Cys336, Gly339, Asn343, Phe342, Leu368, Val367, Ser371, Ser373, Phe374 | -81.34 | -78.90 | -2.44 | 0 | Pro491, Glu471, Arg454, Ser469, Asp467, Tyr473, Phe456, Arg457, Lys458, Ser459, Glu465 |
| **11.** | Losartan | -3.72 | 1.87 mM | Arg466, Ala352, Trp353, Asn354, Arg355, Asp398, Ala397, Ser399, Val341, Glu340, Lys356, Arg357 | -6.7 | 12.36 µM | Val367, Leu368, Ser373, Ser371, Phe374, Asn343, Phe342, Trp436, Arg509, Leu441, Asn440 | -95.21 | -71.08 | -24.13 | 0 | Glu471, Lys458, Ser459, Arg457, Ser469, Asp467, Ile468, Arg454 |

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| **Supplementary Figure 1 (SF1). Best docking poses of WS phytoconstituents with unbound Spike receptor-binding domain (RBD) of SARS-CoV-2 (PDB ID:6M0J) in comparison to the FDA approved standard reference drugs (Arbidol and Losartan)** | | | |
| **Withaferin A** |  |  |  |
| **Withanolide A** |  |  |  |
| **Withanolide B** |  |  |  |
| **Withanolide D** |  |  |  |
| **Withanolide E** |  |  |  |
| **Withanone** |  |  |  |
| **Viscosalactone B** |  |  |  |
| **Anaferine** |  |  |  |
| **Withasomnine** |  |  |  |
| **Arbidol** |  |  |  |
| **Losartan** |  |  |  |