**Supplementary Table 2 (ST2). Binding energies of WS phytoconsituents with SARS-CoV-2 Spike receptor-binding domain (RBD) bound with ACE2 (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 | -8.63 | 474.66 nM | *Phe390, Trp69, Phe40, Arg393, Asn394,* Tyr385, Asp382, Asp350, Trp349, Ala348, Thr347 | -9.9 | 55.88 nM | Ser106, Lys74, Asn103, Ser77, Gln102, Leu391, *Asn394,* Lys562, *Phe390, Trp69, Arg393, Phe40,* Ala99, Leu100, Leu73, Ser70 | -87.22 | -76.74 | -10.49 | 0 | Phe338, Phe342, Asn343, Gly339, Trp436, Asn437, Phe374, Leu368, Ser373 |
| **2.** | Withanolide A | -9.1 | 214.02 nM | *Phe390, Arg393, Asn394,* Tyr385, Asp382, His401, *Asp350,* Glu402, His378, *Ala348, Thr347, Phe40* | -9.3 | 145.58 nM | Ser44, *Arg393,Asn394,* Lys562, Ala99, *Phe390, Phe40,* Leu391, *Asp350, Ala348, Trp349* | -97.11 | -77.09 | -20.02 | 0 | Tyr508, Val407, Arg408, Gly404, Asp405, Tyr505, Gly504, Val593, Gly502, Gly354, Phe356, Thr324 |
| **3.** | Withanolide B | -8.88 | 308.96 nM | Phe40, Ser44, Leu351, Asp350, Trp349, Asp382, His401, His378, Glu402, Glu375, Pro346, *His345,* Thr347, Ala348 | -9.2 | 187.04 nM | Tyr515, Arg273, His505, Phe504, Glu145, Tyr127, Ser128, Leu144, Asn149, Trp271, *His345*, Phe274 | -93.48 | -82.31 | -11.17 | 0 | Gln102, Gln98, Leu95, Lys562, Asp206, Trp203, Gly205, Glu208, Val209, Tyr202, Asn210 |
| **4.** | Withanolide D | -9.38 | 133.07 nM | *Leu391, Lys562, Asn394, Arg393, Phe390, Phe40,* Asp350, Asp382, His401, Ala348 | -10.1 | 38.83 nM | *Phe40,Phe390,* Leu100, Trp69, Leu73, Ala99, *Gln102,Leu391*, Asn103, Ser77, Lys74, Ser70, *Asn394,Arg393,Lys562* | -100.61 | -84.32 | -16.29 | 0 | Gln101, Gln98, *Gln102,* Leu95, *Lys562,* Ala396, Asn397, Asp206, Glu208, Gly205, Tyr196, Asn194 |
| **5.** | Withanolide E | -7.5 | 3.2 µM | Leu391, *Lys562,Asn394,Arg393,Phe390, Phe40, Asp350, Asp382, His401,Ala348* | -9.8 | 62.56 nM | *Asn394, Arg393, Phe390*, Trp69, *Phe40, His401,* Tyr385, *Asp382,* *Asp350, Ala348,* Ser44, Trp349, Ser47 | -102.89 | -87.27 | -15.62 | 0 | Tyr196, Tyr202, Trp203, Gly205, Glu208, Asp206, Val209, Asn397, Pro565, *Lys562,* Glu564, Ala396, Trp566, Leu95, Gln102 |
| **6.** | Withanone | -8.04 | 1.27 µM | Phe390, Arg393, Asn394, Tyr385, Asp382, His401, Glu402, His378, Trp349, Asp350, Phe40, Ala348 | -9.6 | 90.36 nM | Arg514, Tyr510, Trp203, Ser511, Glu398, Tyr196, Gly205, Glu208, Gln98, Leu95, Lys562, Tyr202, Gln102, Asp206 | -93.02 | -75.23 | -17.79 | 0 | Ser511, Arg514, Glu398, Asp206, Gly205, Trp203, Tyr199, Tyr196, Gln102, Glu208, Gln98 |
| **7.** | Viscosalactone B | -8.82 | 341.6 nM | *Phe390, Arg393, Asn394, Phe40*, Asp382, *Asp350,* Trp349, Ala348, Glu402, His378, Thr347, Glu375, Pro346 | -9.5 | 107.69 nM | *Phe40, Phe390,* Tyr385, *Asp350, Arg393, Asn394,* Leu391, Leu73, Gln102, Ala99, Leu100, Asn103, Ser77, Lys74 | -100.63 | -80.65 | -19.98 | 0 | Tyr449, Ser494, Gln493, Gly496, Tyr495, Tyr453, Glu35, Asp38, His34, Glu37, Lys353, Tyr505, Arg403 |
| **8.** | Anaferine | -9.13 | 204.01 nM | *Phe390, Arg393, Tyr385, Asn394, His401, Asp382, Asp350,* Gly352, *Phe40* | -5.9 | 45.93 µM | Leu391, Ala99, *Asp350, Phe40, Arg393, Phe390, Asn394,* Leu73, Trp69 | -76.11 | -64.50 | -11.61 | 0 | *Phe390, Arg393, Tyr385, His401,* His378, *Asp382, Asp350, Phe40,* Ala348 |
| **9.** | Withasomnine | -5.65 | 72.1 µM | Leu391, Asn394, Arg393, Phe390, Asp350, Phe40 | -7.8 | 1.80 µM | *Glu430, Pro415,* Phe428*, Ala413,* Met366, *Phe438, Ile291, Asn290,* Thr434, *Glu435* | -74.91 | -72.32 | -2.59 | 0 | *Asn290, Ile291, Glu430, Pro415, Ala413,* Thr414, *Glu435, Phe438*, Lys541, His540 |
| **10.** | Arbidol | -6.71 | 12.0 µM | Asn394, Tyr385, *His401, Asp382, Phe40,* Ser44, *Asp350, Trp349, Ala348, Thr347*, Glu375, Pro346, His345 | -7.7 | 2.18 µM | Phe390, *Phe40, His401, Asp382, Asp350, Trp349, Ala348, Thr347* | -100.09 | -92.62 | -7.47 | 0 | Gly205, Glu208, Asn210, Val209, Val212, Pro565, Glu564, Ser563, Leu91, Thr92, Leu95, Lys94, Gln98 |
| **11.** | Losartan | -6.44 | 19.09 µM | *Leu391, Phe390, Arg393, Asn394, Tyr385, Asp382, Asp350*, Leu351, Ser44, *Phe40, Trp349, Ala348* | -8.5 | 588. 81 nM | *His401,* His378, *Ala348, Asp350, Asp382, Asn394, Phe390, Phe40, Arg393, Tyr385,* Thr347, *Trp349* | -99.89 | -68.69 | -31.19 | 0 | *His401,* Gly395, *Asn394, Arg393, Leu391, Phe390, Phe40,* Glu37, Gly352, *Asp350, Ala348,* Asp382, *Tyr385* |

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| **Supplementary Figure 2 (SF2). Best docking poses of WS phytoconstituents with SARS-CoV-2 Spike receptor-binding domain (RBD)bound with ACE2(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** |  |  |  |