Targeting the 3CLpro and RdRp of SARS-CoV-2 with phytochemicals from medicinal plants of the Andean region: molecular docking and molecular dynamics simulations

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Supplementary Table 1
Docking scores of tested ligands

| Ligand                          | PUBCHEM or DrugBank ID | Docking score (kcal/mol) to SARS-CoV-2 target | Source in the Andean region | Reference                                                                 |
|---------------------------------|------------------------|-----------------------------------------------|-----------------------------|---------------------------------------------------------------------------|
| 1,3,5-Trimethoxybenzene         | 69301                  | -4.5                                          | Croton lechleri             | (Lock, Perez, Villar, Flores, & Rojas, 2016)                               |
| 18,19-Dihydrocordycepsine       | 3039336                | -6.1                                          | Uncaria tomentosa           | (Gonzales & Valerio, 2006)                                               |
| 246-Trimethoxyphenol            | 88563                  | -6.0                                          | Croton lechleri             | (Lock et al., 2016)                                                      |
| 4-Hydroxycinnamic acid          | 637542                 | -5.1                                          | Clinopodium tomentosum      | (Vera Saltos, Naranjo-Puente, Malafronte, & Braca, 2014)                 |
| 8-prenyldaidzein                | 14841119               | -7.3                                          | Erythrina fusca             | (Khaomek et al., 2008)                                                   |
| Alpha-Pinene                    | 6654                   | -4.3                                          | Minthostachys mollis        | (Torrenegra-Alarcon et al., 2016)                                         |
| Apigenin                        | 5280443                | -7.7                                          | Physalis peruviana          | (El-Beltagi, Mohamed, Safwat, Gamal, & Megahed, 2018)                     |
| Betulinic acid                  | 64971                  | -7.4                                          | Conyza floribunda           | (Manguro, Ogur, & Opiyo, 2010)                                            |
| Bicyclogermacrene               | 13894537               | -5.2                                          | Minthostachys mollis        | (Torrenegra-Alarcon et al., 2016)                                         |
| Byzantiumoside B                | 14135395               | -7.6                                          | Clinopodium tomentosum      | (Vera Saltos et al., 2014)                                               |
| Caffeic acid                    | 689043                 | -5.6                                          | Clinopodium tomentosum      | (Vera Saltos et al., 2014)                                               |
| Carvacrol                       | 10364                  | -4.3                                          | Minthostachys mollis        | (Torrenegra-Alarcon et al., 2016)                                         |
| Compound               | CAS Number | pKa1 | pKa2 | Plant/Species                              | Source                                      |
|------------------------|------------|------|------|--------------------------------------------|---------------------------------------------|
| Cinchonidine           | 101744     | -7.5 | -6.5 | *Cinchona officinalis*                     | (Murauer & Ganzera, 2018)                   |
| Cinchonine             | 90454      | -6.8 | -6.4 | *Cinchona officinalis*                     | (Murauer & Ganzera, 2018)                   |
| Corosolic acid         | 6918774    | -8.7 | -8.3 | *Ugni molinae*                             | (Goity-Vivar, 2013)                         |
| Corynuxoneine          | 44568160   | -6.4 | -6.5 | *Uncaria tomentosa*                        | (Gonzales & Valerio, 2006)                 |
| Cristacarpin           | 126540     | -7.7 | -7.0 | *Erythrina f usca*                         | (Innok, Rukachaisirikul, & Suksamrarn, 2009) |
| Crolechinic acid       | 102237419  | -6.4 | -6.4 | *Croton lechleri*                          | (Lock et al., 2016)                        |
| Cyasterone             | 119444     | -7.9 | -8.0 | *Conyza floribunda*                        | (Manguro et al., 2010)                     |
| Cycloeucalenol         | 101690     | -6.2 | -7.2 | *Croton elegans*                           | (Herrera et al., 2018)                     |
| D-limonene             | 440917     | -4.5 | -4.5 | *Minthostachys mollis*                     | (Torrenegra-Alarcon et al., 2016)          |
| Dolichin A             | 44257432   | -7.5 | -7.3 | *Erythrina f usca*                         | (Innok et al., 2009)                       |
| Dolichin B             | 44257433   | -7.6 | -6.5 | *Erythrina f usca*                         | (Innok et al., 2009)                       |
| Enhydrin                | 5281441    | -6.1 | -6.0 | *Smallanthus sonchifolius*                 | (Lin, Hasegawa, & Kodama, 2003)            |
| Erythrisenegalone      | 15224381   | -7.8 | -7.5 | *Erythrina f usca*                         | (Khaomek et al., 2008)                     |
| Fluctuanin             | 101250074  | -5.8 | -5.8 | *Smallanthus sonchifolius*                 | (Lin et al., 2003)                         |
| Friedelin              | 91472      | -8.3 | -8.2 | *Croton elegans*                           | (Herrera et al., 2018)                     |
| Gallic acid            | 370        | -5.5 | -5.9 | *Physalis peruviana*                       | (El-Beltagi et al., 2018)                  |
| Germacrene-D           | 91723653   | -5.1 | -5.1 | *Minthostachys mollis*                     | (Torrenegra-Alarcon et al., 2016)          |
| Glauicine              | 16754      | -7.1 | -6.3 | *Croton lechleri*                          | (Lock et al., 2016)                        |
| Glucotropaeolin        | 656498     | -7.0 | -6.5 | *Lepidium meyenii*                         | (Sifuentes-Penagos, León-Vázquez, & Paucar-Menacho, 2015) |
| Guaijaverin            | 5481224    | -8.6 | -7.2 | *Bauhinia longifolia*                      | (dos Santos et al., 2014)                  |
| Harmaline              | 3564       | -6.3 | -6.0 | *Banisteriopsis caapi*                     | (Callaway, 2005)                           |
| Hesperetin             | 72281      | -7.3 | -7.0 | *Clinopodium tomentosum*                   | (Vera Saltos et al., 2014)                 |
| Hesperidin             | 10621      | -8.8 | -8.6 | *Psidium guajava*                          | (Trujillo-Correa et al., 2019)             |
| Hirsutine              | 3037884    | -6.5 | -6.5 | *Uncaria tomentosa*                        | (Gonzales & Valerio, 2006)                |
| Hirsuteine             | 3037151    | -6.1 | -6.0 | *Uncaria tomentosa*                        | (Gonzales & Valerio, 2006)                |
| Hyperin                | 5281643    | -8.6 | -7.1 | *Bauhinia longifolia*                      | (dos Santos et al., 2014)                  |
| Chemical Name                  | CAS Number | pKa | pKb | Species/Reference                                      |
|-------------------------------|------------|-----|-----|-------------------------------------------------------|
| Isobavachalcone               | 5281255    | -8.1| -6.6| *Erythrina fusca* (Innok et al., 2009)                |
| Isoboldine                    | 133323     | -7.6| -6.7| *Croton lechleri* (Lock et al., 2016)                 |
| Isocorynioxene                | 3037448    | -7.0| -6.9| *Uncaria tomentosa* (Gonzales & Valerio, 2006)        |
| Isomitraphylline              | 11726520   | -7.2| -7.0| *Conyza floribunda* (Manguro et al., 2010)            |
| Isoquercitrin                 | 5280804    | -8.1| -7.2| *Bauhinia longifolia* (dos Santos et al., 2014)       |
| Isorhynchophylline            | 3037048    | -6.2| -6.9| *Uncaria tomentosa* (Gonzales & Valerio, 2006)        |
| Isorotundifoline              | 102232176  | -6.4| -6.2| *Uncaria tomentosa* (Gonzales & Valerio, 2006)        |
| Kaempferol                    | 5280863    | -7.7| -7.1| *Conyza floribunda* (Manguro et al., 2010)            |
| Korberin A                    | 101926685  | -6.4| -6.9| *Croton lechleri* (Lock et al., 2016)                 |
| Limonene                      | 22311      | -4.4| -4.6| *Minthostachys mollis* (Torrenegra-Alarcon et al., 2016) |
| Lonchocarpol A                | 124035     | -8.0| -7.4| *Erythrina fusca* (Innok et al., 2009)                |
| Longifolol                    | 78265163   | -5.3| -5.5| *Minthostachys mollis* (Torrenegra-Alarcon et al., 2016) |
| Lupinifolin                   | 10250777   | -8.3| -7.6| *Erythrina fusca* (Innok et al., 2009)                |
| Macaridine                    | 636583     | -5.7| -5.6| *Lepidium meyenii* (Sifuentes-Penagos et al., 2015)   |
| Magnoflorine                  | 73337      | -7.6| -6.6| *Croton lechleri* (Lock et al., 2016)                 |
| Mangiferin                    | 5281647    | -8.4| -8.4| *Arrabidae samyooides* (Brandao et al., 2009)         |
| Methylpallidine               | 10405046   | -6.8| -6.4| *Bauhinia longifolia* (dos Santos et al., 2014)       |
| Minquartynoic acid            | 183614     | -5.4| -5.3| *Minquartia guianensis* (de Carvalho-Cursino, Nunez, de Paula, Alves-do Nascimento, & dos Santos, 2012) |
| Mitraphylline                 | 94160      | -7.7| -6.9| *Uncaria tomentosa* (Gonzales & Valerio, 2006)        |
| Myricetin                     | 5281672    | -7.3| -7.1| *Conyza floribunda* (Manguro et al., 2010)            |
| N,N-Dimethyltryptamine        | 6089       | -5.2| -4.9| *Psychotria viridis* (Blackledge & Taylor, 2003)      |
| Naringenin                    | 932        | -7.6| -6.6| *Physalis peruviana* (El-Beltagi et al., 2018)         |
| Neurolobatin A                | 76317958   | -7.3| -6.5| *Neurolaena lobata* (Lajter et al., 2014)              |
| Neurolobatin B                | 76332514   | -7.4| -6.4| *Neurolaena lobata* (Lajter et al., 2014)              |
| Norisoboldine                 | 14539911   | -7.8| -6.9| *Croton lechleri* (Lock et al., 2016)                 |
| Notholaenic acid              | 3085829    | -7.2| -6.3| *Notholaena nivea* (Cioffi et al., 2011)               |
| Compound                  | CAS Number | pH1 | pH2 | Plant(s)                                                                 |
|---------------------------|------------|-----|-----|---------------------------------------------------------------------------|
| Oleanolic acid            | 10494      | -7.7| -8.3| *Minquartia guianensis*                                                 |
|                           |            |     |     | *Uncaria tomentosa*                                                       |
| Pallidine                 | 12313923   | -7.0| -6.9| *Bauhinia longifolia*                                                    |
| Phaseollidin              | 119268     | -7.4| -7.2| *Erythrina fusca*                                                         |
| Pinocembrin 7-O-rutinoside| 189596     | -8.5| -8.8| *Clinopodium tomentosum*                                                 |
| Pulegone                  | 442495     | -5.0| -4.9| *Minthostachys mollis*                                                   |
| Quercetin                 | 5280343    | -7.3| -7.3| *Bauhinia longifolia*                                                    |
| Quercitrin                | 5280459    | -9.0| -8.0| *Bauhinia longifolia*                                                    |
| Quinidine                 | 441074     | -6.8| -6.4| *Cinchona officinalis*                                                   |
| Quinine                   | 3034034    | -7.0| -6.6| *Cinchona officinalis*                                                   |
| Rhynchophylline           | 5281408    | -6.4| -6.3| *Uncaria tomentosa*                                                      |
| Rosmaniric acid           | 5281792    | -7.8| -6.3| *Clinopodium tomentosum*                                                 |
| Rotundifoline             | 139055911  | -6.6| -6.2| *Uncaria tomentosa*                                                      |
| Rutin                     | 5280805    | -8.9| -8.5| *Croton lechleri*                                                        |
|                           |            |     |     | *Physalis peruviana*                                                      |
| Sandwicensin              | 467498     | -7.1| -6.6| *Erythrina fusca*                                                        |
| Sinoacutin                | 821366     | -7.3| -6.6| *Croton lechleri*                                                        |
| Speciophylline            | 168985     | -7.2| -7.7| *Uncaria tomentosa*                                                      |
| Squalene                  | 638072     | -5.9| -4.6| *Minquaria guianensis*                                                   |
| Stigmasterol              | 5280794    | -7.1| -7.3| *Lepidium meyenii*                                                       |
|                           |            |     |     | *Uncaria tomentosa*                                                      |
| Taspine                   | 215159     | -7.7| -6.9| *Croton lechleri*                                                        |
| Tetrhydroalstonine        | 72340      | -7.5| -7.2| *Uncaria tomentosa*                                                      |
| Thaliporphine             | 100020     | -7.3| -6.4| *Croton lechleri*                                                        |
| Tomentoside               | 101664499  | -7.5| -6.9| *Uncaria tomentosa*                                                      |
| Uncarine B                | 12304286   | -7.6| -7.2| *Uncaria tomentosa*                                                      |
| Compound         | Code     | logP   | logD   | Species                  | Literature                          |
|------------------|----------|--------|--------|--------------------------|-------------------------------------|
| Uncarine C       | 10429112 | -7.9   | -6.9   | Uncaria tomentosa        | (Gonzales & Valerio, 2006)          |
| Uncarine F       | 12304288 | -7.6   | -6.5   | Uncaria tomentosa        | (Gonzales & Valerio, 2006)          |
| Uvedalin         | 73353398 | -6.4   | -6.5   | Uncaria tomentosa        | (Gonzales & Valerio, 2006)          |
| Vitexin          | 5280441  | -8.1   | -8.9   | Croton lechleri          | (Lock et al., 2016)                 |
| Wighteone        | 5281814  | -7.3   | -7.0   | Erythrina fusca          | (Pino-Rodriguez et al., 2004)       |
| Chloroquine      | 2719     | -6.0   | -5.0   |                          |                                     |
| Hydroxychloroquine | 3652   | -6.3   | -5.6   |                          |                                     |
| Darunavir        | DB01264  | -7.7   | -7.9   |                          |                                     |
| Lopinavir        | DB01601  | -7.9   | -6.9   |                          |                                     |
| Nelfinavir       | DB00220  | -8.3   | -7.9   |                          |                                     |
| Paritaprevir     | DB09297  | -10.3  | -12.3  |                          |                                     |
| Remdesivir       | DB14761  | -8.2   | -7.5   |                          |                                     |
| Ritonavir        | DB00503  | -8.2   | -7.2   |                          |                                     |
| Saquinavir       | DB01232  | -7.8   | -7.6   |                          |                                     |
| Sotrosvir        | DB12051  | -9.4   | -8.7   |                          |                                     |
| Simeprevir       | DB06290  | -9.3   | -9.3   |                          |                                     |
| Sofosbufir       | DB08934  | -8.1   | -7.4   |                          |                                     |
Figure S1. Backbone root mean square deviation (RMSD) of the 3CLpro (A) and RdRp (B) of SARS-CoV-2 in complex with phytochemicals, during 200 ns of the molecular dynamics simulation period. Backbones with mean RMSD higher than free protein are plotted.

Figure S2. Backbone root mean square deviation (RMSD) of phytochemicals from complexes with 3CLpro (A) and RdRp (B), during 200 ns of the molecular dynamics simulation period.
Figure S3. Conformational evolution of secondary structure elements of 3CLpro in complex with hesperidin (A) and lupinifolin (B) during the molecular dynamics simulation period.
Figure S4. Conformational evolution of secondary structure elements of RdRp in complex with hesperidin during the molecular dynamics simulation period.
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