Supplementary material:

In silico identification of natural antiviral compounds as a potential inhibitor of Chikungunya Virus non-structural protein 3 macrodomain

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The list of the compounds, based on the binding affinity (Vina scores) of the highest-ranked position in the ligand docked with CHIKV nsP3MD is shown in Table S1. From the natural compounds, five compounds (Baicalin, Berberine, Quercetin, Curcumin, and Apigenin) were the only compound that has already been tested in vivo against CHIKV (Table S1 and Table S2). Additionally, the remaining twenty-six plant-based natural compounds (Narirutin, Scutellarin, Complanatuside, Eriocitrin, Rutacearpine, Amentoflavone, Apigenin, OroxinB, Luteoloside, Baloxavir, Homoorientin, Withanolide, Withaferin A, Sitosterol, Astragalin, Piperine, Nicotiflorin, Gingerol, Cannabidiol, Aloesin, Dehydroandrographolide, Aloenin, Shogaol, Nimbin, Lupeol, and Ursolic acid have not been tested in vivo against CHIKV.

Binding score of eleven synthetic compounds; Umbralisib, Bictegravir, Sofosbuvir, Pimobendan, Verdinexor, Aprepitant, Amenamevir, Dolutegravir, Indigo, GSK650394, and Dapivirine were -11.1, -10.7, -10.5, -10.4, -10.3, -10.2, -10.2, -10.1, -10.1, -10.0, -10.0 kcal/mol, respectively (Table S1 and Table S2).

Top screened inhibitor Umbralisib is under clinical trial Phase 2 (Table S2). Second top-scoring, Sofosbuvir, a synthetic drug, is already used for the treatment of HCV (Table S1 and Table S2). However, Sofosbuvir demonstrated relevant results (with an EC50 of 11µm) in vivo in decreasing viremia or in reducing clinical manifestations during CHIKV infection (Ferreira et al. 2019).
Figure S1: 2D structure of other eleven synthetic compounds identified through CHIKV nsP3MD docking study visualized using maestro (Schrödinger). All 2D structures are representing with compound number, compound name and binding affinity in (kcal/mol).
25. Withanolide (-9.4)
26. Withaferin A (-9.3)
29. Sitosterol (-8.7)
31. Astragalin (-8.4)
32. Piperine (-8.3)
33. Nicotiflorin (-8.2)
34. Gingerol (-7.9)
35. Cannabidiol (-7.8)
36. Aloesin (-7.6)
37. Dehydroandrographolide (-7.6)
38. Aloenin (-7.4)
39. Shogao (-7.3)
40. Nimbin (-7.1)
41. Lupeol (-7.0)
42. Ursolic acid (-6.8)
**Figure S2:** 2D structure of other fifteen natural compounds used for CHIKV nsP3\textsuperscript{MD} docking study visualized using maestro (Schrödinger). All 2D structures are representing with compound number, compound name and binding affinity in (kcal/mol).

24. Berberine (-9.5)  
27. Quercetin (-8.9)  
28. Curcumin (-8.8)  
30. Apigenin (-8.4)

**Figure S3:** 2D structure of four natural compounds showed anti CHIKV activity used four CHIKV nsP3\textsuperscript{MD} docking study visualized using maestro (Schrödinger). All 2D structures are representing with compound number, compound name and binding affinity in (kcal/mol).
| Compound number | Binding Affinity (kcal/mol) | H-Bonds (Residue (Atom Number-Distance in Å-Ligand atom number) Ligand) | Other Interactions (Total Hydrophobic Interacting Residues) |
|-----------------|-----------------------------|-------------------------------------------------------------------------|----------------------------------------------------------|
| 1. Umbralisib   | -11.1                       | B-Leu108(O-2.74-05)L, S-Thr111(O-2.80-03)L, B-Thr114(N-3.11-F3)L, Asp144(NH2-2.68-O1)L | Asp10, Ile11, Ala22, Ala23, Asp31, Val33, Pro107, Leu109, Val113, Tyr114, Trp148 (I2) |
| 2. Baicalin     | -10.8                       | B-Met9(O-3.29-09)L, B-Leu108(O-2.48-01)L, S-Thr111(O-2.96-02)L, B-Thr114(N-2.83-O11)L, Asp144(NH2-2.94-O7)L, | Ile11, Ala22, Asn24, Asp31, Gly30, Gly32, Val33, Pro107, Leu109, Gly112, Val113, Tyr142, Tyr142 (I3) |
| 3. Narirutin    | -10.8                       | B-Met9(O-3.12-014)L, B-Ile11 (N-2.98-014)L, S-Asn24(ND2-2.83-06)L, B-Gly32(N-2.76-011)L, B-Leu108(O-2.79-05)L, B-Thr111(O-2.80-03)L, B-Gly112(N-3.11-O3)L, B-Arg144(N-2.87-O11)L, B-Arg144(NH1-2.80-09)L, B-Arg144(NH1-2.97-O10)L | Asp10, Ala22, Ala3, Val33, Cys34, Lys35, Ala36, Leu109, Tyr144, Tyr142, Cys143 (I2) |
| 4. Bictegravir  | -10.7                       | B-Leu108(O-3.13-05)L, B-Ser110(N-3.26-05)L, B-Thr111(O-2.94-03)L, B-Arg144(NE-3.26-F1)L, B-Arg144(NB2-3.28-F1)L | Met9, Ile11, Ala22, Ala23, Gly32, Val33, Cys34, Leu109, Gly112, Val113, Tyr144, Tyr142, Cys143 (I3). |
| 5. Scutellarin  | -10.7                       | B-Met9(O-3.14-O7)L, S-Asn24(ND1-2.77-O12)L, B-Leu108(O-2.72-014)L | Asp10, Ala22, Ala3, Gly32, Val33, Ala36, Leu109, Val113, Tyr144, Tyr142, Cys143 (I2). |
|   | **Compound** | **Interaction** | **Results** |
|---|-------------|----------------|-------------|
| 6. | Complanat side | B-Ser110(N-2.83-O1)L, B-Thr111(N-3.12-O11)L, B-Thr111(N-3.32-O1)L, S-Thr111(OG1-2.79-O11)L, S-Thr111(OG1-3.33-O10)L, B-Gly112(N-2.95-O11)L, S-Arg144(NH1-3.17-O7)L | Ala22, Val33, Cys34, Ala36, Leu109, Ser110, Gly12, Val113, Tyr114, Tyr142, Cys143, Trp148 (12), \(\text{Thr142} \) (9) |
| 7. | Sofosbuvir | B-Met9(O-2.84-O12)L, B-Met9(O-3.21-O13)L, B-Ile11(N-3.02-O13)L, S-Asp10(OD1-3.23-O14)L, S-Asp10(OD1-3.11-O13)L, B-Gly32(O-3.29-O13)L, B-Gly32(NB1-2.81-O13)L, B-Arg144(N-3.11-O1)L, B-Arg144(N-3.01-O15)L, S-Arg144(NH2-2.81-O13)L, B-Asp145(N-3.02-O15)L | Met9, Ile11, Ala22, Ala23, Asp31, Val33, Cys34, Ser110, Leu108, Tyr114, Tyr142, Cys143, Trp148 (13) |
| 8. | Verdinexor | B-Asp31(O-3.09-N2)L, B-Gly70(N-3.16-F2)L, B-Ser10(N-2.96-F1)L, B-Ser10(N-3.22-F3)L | Met9, Ile11, Ala22, Ala23, Gly32, Val33, Gly112, Val113, Tyr114, Tyr142, Cys143, Arg144 |
| 9. | Pimobendan | S-Asn24(ND2-3.05-O5)L, B-Thr111(N-3.29-O3)L, S-Gly112(N-2.95-O3)L, S-Cys143(N-3.89-O7)L, B-Asp145(N-3.11-O7)L | Ala22, Ala23, Cys34, Ser110, Gly112, Tyr114, Tyr142, Cys143, Trp148 (9) |
| 10. | Eriocitrin | B-Met9(O-3.08-O14)L, S-Asp10(OD1-2.94-O15)L, B-Ile11(N-3.90-O15)L, S-Asn24(ND1-3.04-O6)L, B-Asp31(O-3.22-O5)L, B-Leu108(O-2.86-O7)L, S-Thr111(OG1-2.36-O7)L, B-Thr111(N-2.85-O4)L, B-Gly112(N-3.10-O5)L, B-Ser110(N-3.07-O5)L, S-Arg144(ND2-2.63-O9)L | Ala22, Ala23, Gly30, Gly32, Val33, Cys34, Lys35, Ala36, Lys39, Leu109, Cys143 (11) |
| 11. | Rutaecarpine | S-Thr111(N-2.97-O1)L, B-Gly112(N-3.17-O1)L | Ala22, Asn24, Gly30, Asp31, Gly32, Val33, Cys34, Leu108, Leu109, Ser110, Tyr114 (11) |
| 12. | Aprepitant | S-Asn24(ND2-3.22-F4)L, B-Val33(N-3.17-O3)L, S-Cys34(SG-3.34-F4)L, B-Ser110(N-3.08-F1)L, B-Ser110(N-3.10-F2)L, B-Arg144(N-2.92-O3)L | Ala22, Ala23, Asp31, Gly32, Leu108, Thr111, Gly112, Val113, Tyr114, Cys143, Trp148 (11) |
| 13. | Amentoflavone | B-Ala23(O-2.67-O9)L, S-Asn24(ND2-3.19-O10)L | Met9, Asp10, Ala22, Asp31, Gly30, Gly32, Val33, Lys35, Gly112, Val113, Tyr114, Tyr142, Cys143, Arg144 (14) |
| 14. | Amenamivir | S-Asn24(ND2-3.08-O3)L, B-Ala22(O-2.80-N3)L | Ala23, Asp31, Gly32, Val33, Cys34, Leu108, Thr111, Gly112, Val113, Tyr114, Tyr142, Cys143, Arg144, Trp148 (14) |
| 15. | Dolutegravir | -10.1 | B-Ser110(O-2.86-O3)L | Ala22, Ala23, Asp31, Gly32, Leu108, Leu109, Thr111, Gly112, Val113, Tyr114, Asp145, Trp148 (12). |
| 16. | Indigo | -10.1 | B-Val33(N-3.28-O1)L, B-Leu108(O-3.26-N1)L, B-Ser110(N-3.06-O2)L, S-Thr111(OG1-3.17-N1)L, B-Thr111(N-2.97-O2)L, B-Gly112(N-3.12-O2)L | Ala22, Asp31, Gly32, Leu109, Tyr114, Cys143, Arg144 (7). |
| 17. | Apigetrin | -10.1 | B-Met9(O-2.81-O8)L, S-Asn24(ND2-2.92-O10)L, B-Ile11(N-3.09-O7)L, B-Leu108(O-2.81-O1)L, B-Ser110(N-2.94-O1)L, B-Thr111(N-2.88-O9)L, S-Thr111(OG1-2.39-O9)L, B-Gly112(N-3.18-O1)L, B-Cys143(O-3.13-O8)L | Asp10, Ala22, Ala23, Asp31, Gly32, Val33, Cys34, Leu109, Tyr114, Tyr142, Arg144 (11). |
| 18. | Oroxin B | -10.1 | B-Ala22(O-2.76-O10)L, B-Leu108(O-3.96-O15)L, B-Ser110(N-2.92-O13)L, B-Ser110(N-2.96-O12)L, S-Thr111(OG1-2.78-O14)L, S-Thr111(OG1-2.93-O15)L, B-Thr111(N-3.13-O13)L, B-Gly112(N-3.34-O13)L, S-Arg144(ND2-3.28-O3)L | Asp10, Ala23, Asp31, Gly32, Val33, Cys34, Lys35, Ala36, Lys39, Leu109, Tyr114, Cys143, Trp148 (13). |
| 19. | Baloxavir | -10.0 | B-Ser110(N-3.05-O3)L, B-Thr114(N-3.01-O6)L, B-Gly112(N-2.80-O6)L | Ala22, Asp31, Gly32, Val33, Leu108, Thr111, Val113, Thr142, Arg144, Trp148 (10). |
| 20. | GSK650394 | -10.0 | B-Tyr142(O-3.32-N1)L | Ala22, Asp31, Gly32, Val33, Pro107, Leu108, Ser110, Thr111, Val113, Tyr114, Cys143, Asp145, Trp148 (13). |
| 21. | Dapivirine | -10.0 | B-Leu108(O-3.28-N3)L, B-Leu108(O-3.33-N5)L, S-Thr111(OG1-2.86-N3)L | Ala22, Ala23, Asn24, Val33, Val113, Tyr114, Gly112, Tyr142, Cys143, Arg144, Asp145, Trp148 (12). |
| 22. | Homoorie | -10.0 | S-Asn24(ND2-2.89-O11)L, B-Leu108(N-3.12-O7)L, B-Ser110(N-2.96-O2)L, S-Thr111(OG1-3.75-O8)L, B-Thr111(N-3.08-O2)L, B-Gly112(N-3.30-O2)L, B-Arg144(N-3.17-O5)L | Ala22, Ala23, Gly30, Asp31, Gly32, Val33, Leu109, Val113, Tyr114, Tyr142, Cys143, Asp145, Trp148 (13). |
| 23. | Luteoloside | -10 | B-Met9(O-3.15-O6)L, S-Asp10(OD1-3.34-O6)L, B-Ile11(N-2.88-O6)L, S-Asn24(ND2-2.73-O11)L, S-Arg32(O-3.05-O5)L, B-Ser110(N-2.96-O2)L, B-Gly112(N-2.95-O9)L, B-Thr111(N-3.13-O9)L, S-Thr111(OG1-2.66-O9)L, S-Arg144(NB2-3.10-O6)L, B-Arg144(NH2-3.22-O8)L | Ala22, Ala23, Asp31, Ala36, Leu108, Val113, Tyr114, Val153, Tyr142, Cys143 (10). |

Other plant based natural compounds

| 24. | Berberine | -9.5 | | Ala22, Asn24, Asp31, Gly32, Val33, Cys34, Leu108, Ser110, Thr111, Gly112, Tyr114, Tyr142, Arg144 (13). |
| No. | Compound         | Value  | Structure 1 | Structure 2 |
|-----|-----------------|--------|-------------|-------------|
| 25. | Withanolide     | -9.4   | B-Val33(N-2.79-O3)L, B-Ser10(N-2.80-O5)L, B-Asp145(N-2.57-O6)L | Ala22, Ala23, Asp24, Asp31, Gly32, Leu108, Leu109, Thr111, Gly112, Val113, Tyr114, Arg144, Trp148 (13) |
| 26. | Withaferin A    | -9.3   | B-Ala22(O-3.31-O2)L, B-Arg144(N-2.96-O6)L, B-Asp145(N-2.54-O6)L | Ala23, Asp24, Asp31, Gly32, Val33, Leu108, Thr111, Gly112, Val113, Tyr114, Cys143, Trp148 (12) |
| 27. | Quercetin       | -8.9   | B-Asp31(N-3.21-O3)L, S-Ala22(ND2-2.92-O4)L, B-Leu108(O-2.84-O6)L, B-Ser110(N-2.98-O2)L, B-Thr111(N-2.80-O2)L, S-Thr111(OG1-2.51-O6)L, B-Gly112(N-3.05-O2)L | Ala22, Ala23, Gly30, Gly32, Val33, Cys34, Leu109, Tyr114 (8) |
| 28. | Curcumin        | -8.8   | B-Met9(O-3.02-O3)L, B-Ile11(N-2.99-O3)L, S-Arg144(NE-2.88-O2)L, S-Arg144(NB1-3.03-O2)L, S-Arg144(NB1-2.85-O3)L | Asp10, Ala22, Asp24, Asp31, Gly32, Val33, Cys34, Leu108, Thr111, Gly112, Val113, Tyr114, Cys143, Tyr142 (15) |
| 29. | Sitosterol      | -8.7   | S-Asn24(ND2-2.97-O3)L, B-Leu108(O-2.72-O4)L, B-Ser110(N-2.92-O2)L, B-Thr111(N-2.96-O2)L, S-Thr111(OG1-2.70-O4)L, B-Gly112(N-3.16-O2)L | Ala22, Ala23, Asp31, Gly32, Val33, Leu108, Ser110, Thr111, Gly112, Val113, Tyr114, Arg144, Asp145, Trp148 (14) |
| 30. | Apigenin        | -8.4   | B-Val33(N-3.11-O1)L, B-Leu108(O-2.93-O10)L, B-Gly112(O-3.02-O10)L, B-Ser110(N-3.09-O10)L, B-Thr111(N-2.81-O10)L, B-Thr111(O-3.04-O8)L, S-Thr111(OG1-2.70-O2)L, S-Thr111(O1-3.25-O8)L, S-Arg144(NE-2.88-O9)L | Ala22, Ala23, Asp31, Gly32, Val33, Leu109, Val113, Tyr114 (8) |
| 31. | Astragaline     | -8.3   | B-Val33(N-3.11-O1)L, B-Leu108(O-2.93-O10)L, B-Gly112(O-3.02-O10)L, B-Ser110(N-3.09-O10)L, B-Thr111(N-2.81-O10)L, B-Thr111(O-3.04-O8)L, S-Thr111(OG1-2.70-O2)L, S-Thr111(O1-3.25-O8)L, S-Arg144(NE-2.88-O9)L | Ala22, Asp31, Gly32, Leu109, Trp148 (5) |
| 32. | Piperine        | -8.3   | S-Asp10(OD1-3.04-O6)L, B-Ala22(O-2.80-O11)L, B-Asp31(O-2.70-O13)L, B-Asp31(O-2.68-O12)L, B-Cys34(N-3.00-O12)L, B-Leu108(O-2.68-O15)L, B-Val113(N-3.10-O10)L, B-Tyr142(O-2.50-O14)L, S-Arg144(NE2-2.94-O6)L | Gly32, Val33, Lys35, Ala36, Pro107, Gly112, Tyr114, Cys143, (11) |
| 33. | Nicotiflorin    | -8.2   | B-Ile11(OG1-3.12-O4)L, B-Leu108(O-2.81-O2)L, B-Thr111(N-2.88-O2)L, B-Gly112(N-3.04-O2)L, S-Arg144(NE-2.99-O3)L | Met9, Asp10, Ala22, Ala23, Val33, Leu109, Ser110, Thr111, Tyr114, Cys143, (10) |
| 34. | Gingerol        | -7.9   | B-Ile11(OG1-3.12-O4)L, B-Leu108(O-2.81-O2)L, B-Thr111(N-2.88-O2)L, B-Gly112(N-3.04-O2)L, S-Arg144(NE-2.99-O3)L | Met9, Asp10, Ala22, Ala23, Val33, Leu109, Ser110, Thr111, Tyr114, Cys143, (10) |
| 35. | Cannabidiol     | -7.8   | S-Thr111(OG1-2.83-O2)L | Ala22, Ala23, Asp31, Gly32, Val33, Pro107, Leu108, Gly112, Tyr114, Cys143, Arg144, Trp148 (13) |
| 36. | Aloesin         | -7.6   | B-Asp31(O-2.99-O6)L, B-Val33(N-2.89-O7)L, B-Val33(N-2.82-O6)L | Ala22, Gly32, Pro107, Thr111, Val113, Tyr114, Cys143, Trp148 (9) |
| 37. | Dehydroandro grapholide | -7.6 | B-Leu108(O-2.74-O8)L, B-Gly112(N-3.15-O3)L, B-Ser110(N-3.20-O4)L | Gly32, Val33, Tyr114, Cys143, Arg144, Trp148 (6) |
| 38. | Aloenin | -7.4 | B-Asp31(O-3.06-O5)L, B-Ser110(N-3.13-O3)L, B-Leu108(N1-2.93-O8)L, B-Thr111(N-3.12-O3)L, B-Gly112(N-3.31-O3)L | Met9, Ile11, Gly32, Val33, Pro107, Leu109, Val113, Tyr142, Cys143, Arg144, Trp148 (11) |
| 39. | Shogaol | -7.3 | B-Met9(O-2.98-O3)L, B-Ile11(N-3.15-O3)L, S-Arg144(NE-2.85-O2)L, S-Arg144(NB2-3.27-O2)L, S-Arg144(NB2-3.18-O2)L | Asp10, Ala22, Gly32, Val33, Leu108, Thr111, Gly112, Val113, Tyr114, Tyr142, Cys143 (11) |
| 40. | Nimbin | -7.1 | S-Arg144(NE-3.28-O3)L, S-Arg144(NE-3.02-O3)L, B-Asp145(N-3.02-O7)L | Asp10, Ile11, Gly32, Val33, Ala36, Thr111, Cys143, Trp148 (8) |
| 41. | Lupeol | -7.0 | B-Asp145( N-2.96-O1)L | Gly32, Lys35, Leu108, Thr111, Gly112, Tyr142, Cys143, Arg144, Trp148 (9) |
| 42. | Ursolic acid | -6.8 | Ala22, Asp31, Gly32, Val33, Leu108, Thr111, Gly112, Val113, Arg144, Trp148 (10) |

**Abbreviations:** S-Side chain, B-backbone, L-ligand. The Residues indicated in red color are mutated residues in previous study (Abraham et al., 2018; Alhammad & Fehr, 2020). It was shown that mutations Val33 and Asp10 of the CHIKV MD, which likely impair both ADP-ribose binding and hydrolysis (Eckei et al., 2017; McPherson et al., 2017).
Molecular interactions of Narirutin, Scutellarin, Complanatuside, Eriocitrin, Oroxin B and Homoorientin

Narirutin is also identified as a strong binder of the CHIKV nsP3\textsuperscript{MD}. Results showed -10.8 kcal/mol binding energy with CHIKV nsP3\textsuperscript{MD} and interacted with nsP3\textsuperscript{MD} through twelve hydrogen bonds with nine residues Met9, Ile11, Asn24, Gly32, Leu108, Ser110, Thr111, Gly112 and Arg144 along with twelve hydrophobic interactions with Asp10, Ala22, Ala23, Asp31, Val33, Cys34, Lys35, Ala36, Leu109, Tyr114, Tyr142, and Cys143 residues (Table S1).

Scutellarin showed -10.8 kcal/mol binding energy with CHIKV nsP3MD and bound with nsP3MD through ten hydrogen bonds with seven residues Met9, Asn24, Leu108, Ser110, Thr111, Gly112 and Arg144 along with twelve hydrophobic interactions with Asp10, Ala22, Ala23, Asp31, Gly32, Val33, Ala36, Leu109, Val113, Tyr114, Tyr142 and Cys143 residues (Table S1).

Complanatuside showed -10.5 kcal/mol binding energy with CHIKV nsP3MD and bound with nsP3MD through eleven hydrogen bonds with seven residues Met9, Asp10, Ile11, Gly32, Ala36, Arg144 and Asp145 along with twelve hydrophobic interactions with Ala22, Val33, Cys34, Ala36, Leu109, Ser110, Gly112, Val113, Tyr114, Tyr142, Cys143 and Trp148 residues (Table S1).

Eriocitrin showed -10.4 kcal/mol binding energy with CHIKV nsP3MD and bound with nsP3MD through eleven hydrogen bonds with ten residues Met9, Asp10, Ile11, Asn24, Asp31, Leu108, Ser110, Thr111, Gly112 and Arg144 along with eleven hydrophobic interactions with Ala22, Ala23, Gly30, Gly32, Val33, Cys34, Lys35, Ala36, Lys39, Leu109 and Cys143 residues (Table S1).

Oroxin B showed -10.1 kcal/mol binding energy with CHIKV nsP3MD and bound with nsP3MD through nine hydrogen bonds with six residues Ala22, Leu108, Ser110, Thr111, Gly112 and Arg144 along with thirteen hydrophobic interactions with Asp10, Ala23, Asp31, Gly32, Val33, Cys34, Lys35, Ala36, Lys39, Leu109, Tyr114, Cys143 and Trp148 residues (Table S1).

Homoorientin showed a -10.0 kcal/mol binding energy with CHIKV nsP3\textsuperscript{MD} and bound with nsP3\textsuperscript{MD} through seven hydrogen bonds with six residues Asn24, Leu108, Ser110, Thr111, Gly112 and Arg144 along with thirteen hydrophobic interactions with Ala22, Ala23, Gly30, Asp31, Gly32, Val33, Leu109, Val113, Tyr114, Thr142, Cys143, Asp145 and Trp148 residues (Table S1).
| S.no | Ligand   | Target Information and properties | Trade Name or Brand name | Company | Clinical trial | rCHIKV NP3 MD study (Yes/No) | CHIKV activity tested (Yes/No) | Compound (Synthetic/Natural) | References                                                                 |
|------|----------|----------------------------------|--------------------------|---------|----------------|-----------------------------|------------------------------|-----------------------------|----------------------------------------------------------------------------|
| 1.   | Umbralisib | Chronic Lymphocytic Leukemia    | -                        | -       | Phase 2        | No                          | No                           | Synthetic                   | (Clinicaltrials, n.d.)                                                   |
| 2.   | Baicalin | nsP3                             | -                        | -       | -              | No                          | Yes                          | Natural                     | (Oo et al., 2018; Seyedi et al., 2016; Tao et al., 2018)(Wang et al., 2020) |
| 3.   | Narirutin | Anti-inflammatory and anti-oxidative effects | -                        | -       | -              | No                          | No                           | Natural                     | (Salehi et al., 2019)                                                    |
| 4.   | Scutellarin | antioxidant, antitumor, antiviral, and antiinflammatory activities. | -                        | -       | -              | No                          | No                           | Natural                     | (Chan & , Carine S. S. Lim, Win Yee Lim, Zhi Juin Loong, 2019)             |
| 5.   | Bictegavir | HIV-1 integrase                  | Biktarvy                 | Gilead’s | -              | -                           | -                            | Synthetic                   | (Hughes, 2019)                                                          |
| 6.   | Complanatuside | Anti-inflammation, lipid-lowering and hepatoprotective effects. | Sovaldi              | Gilead Sciences, Inc. | - | No (nsP4) | Yes Inhibition | Synthetic | (Ferreira et al., 2019)  |
| 7.   | Sofosbuvir | HCV NS5B polymerase inhibitor     | -                        | -       | Phase 2        | No                          | No                           | Synthetic                   | (Nandedkar et al., 2020)                                                 |
| 8.   | Verdinexor | Selective XPO1/CRM1 inhibitor.    | -                        | -       | -              | No                          | No                           | Synthetic                   | (Nieminen et al., 2000)                                                  |
| 9.   | Pimobendan | Cardiac drug for oral use in dogs only | Vetmedi n®                | Boehringer Ingelheim | - | No       | No                     | Synthetic                   | (Cesari et al., 2020)                                                   |
| 10.  | Eriocitrin | Antioxidant activity              | --                       | -       | -              | -                           | -                            | Natural                     | (Tian, Li, & Xu, 2019)                                                   |
| 11.  | Rutaecarpine | COX-2 inhibitor                   | -                        | -       | -              | -                           | -                            | Natural                     | (Muñoz, Crespo Carlos, Crespo)                                             |
| 12.  | Aprepitant | Neurokinin-1 receptor, HIV,,antiemetics | Emend                  | Dheer Healthcare | - | No       | No                     | Synthetic                   | (Muñoz, Crespo Carlos, Crespo)                                             |
|   |   |   |   |   |   |
|---|---|---|---|---|---|
| 13. | Amenamevir | *Herpes zoster*, HSV-1 helicase-primase inhibitor | Amenali ef Maruho (Originator) | Phase III | No |
| 14. | Amentoflavone | Antibacterial, antioxidant, antiviral, antidiabetic, and neuroprotective activities | Amento Max Analyzed Supplements | - | - |
| 15. | Dolutegravir | HIV integrase inhibitor | Tivicay ViiV Healthcare | Phase 2 | No |
| 16. | Indigo | - | - | - | No |
| 17. | Apigetrin | Antimutagenic, anticancer, antioxidant and anti-inflammatory properties. | - | - | No |
| 18. | OroxinB | Therapeutic agent for liver cancer, COX-2, VEGF, PI3K, and p-AKT | Xofluza ®) Shionogi Co., and Roche AG | - | No |
| 19. | Baloxavir | Influenza A and influenza B cap-dependent endonuclease enzyme inhibitor | - | - | No |
| 20. | GSK650394 | Glucocorticoid-regulated kinase-1 inhibitor | - | - | No |
| 21. | Dapivirine | HIV reverse transcriptase | Phase III | No |
|   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|
|   |   |   |   |   |   |   |
| 22. | Homoorientin | Radical scavenger and an antineoplastic agent | - | - | - | No | Natural | (Quílez, Fernández-Arche, García-Gimenez, & Puerta, 2018) |
| 23. | Luteoloside | Anti-microbial and anti-cancer activities, 3C Protease of Enterovirus 71 | - | - | - | No | Natural | (Shi, He, Zhao, & Wang, 2020) |

**Other natural compounds**

|   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|
| 24. | Berberine | Antibacterial, anti-inflammatory and antioxidant properties | Berberine | EzyAbsorb | - | Yes | Natural | (Ghildiyal & Gabrani, 2020; Kovacikova & van Hemert, 2020) |
| 25. | Withanolide | Hypnosedative, immunomodulatory, anti-inflammatory, antiarthritic, angiogenesis inhibitor, anticholinesterase, antioxidant, antibacterial and, antitumour | - | - | - | - | Natural | (Dutta, Khalil, Green, Mohapatra, & Mohapatra, 2019) |
| 26. | Withaferin A | Anti-leukemic, anti-invasive, anti-metastatic, apoptotic, anti-inflammatory, radiosensitizing and antidiabetic activity | - | - | - | - | Natural | (Kumar et al., 2020; Pandey et al., 2018) |
| 27. | Quercetin | 5-ethyl-2-dioxyuridine and acyclovir against HSV and pseudorabies infection | Quercetin (BCM-95) | Webber Naturals | - | Yes Inhibition | Natural | (Lalani & Poh, 2020; Wang et al., 2020) (Subudhi, Chattopadhyay, Mishra, & Kumar, 2018) |
| 28. | Curcumin | Antiviral properties | Curcumin (BCM-95) | - | Yes Inhibition | Natural | (Ghildiyal & Gabrani, 2020; Kovacikova & van Hemert, 2020) |
| No. | Name     | Activity                                                                 | Source                                      | Type                          | Reference                                                                 |
|-----|----------|--------------------------------------------------------------------------|---------------------------------------------|-------------------------------|--------------------------------------------------------------------------|
| 29. | Sitosterol | Used for lowering cholesterol levels and reduce swelling (inflammation). | Mega strength beta sitosterol              | -                             | Natural                                                                   | Hemert, 2020; Mathew & Hsu, 2018; Mounce, Cesaro, Carrau, Vallet, & Vignuzzi, 2017; Subudhi et al., 2018 |
| 30. | Apigenin  | Inhibitor for CYP2C9 and anti CHIKV                                      | Apigenin Prostrate health                   | -                             | Yes Inhibition                                                           | Kovacikova & van Hemert, 2020; Lalani & Poh, 2020; Subudhi et al., 2018; Wang et al., 2020 |
| 31. | Astragalin| Anti-tumor, anti-inflammatory and antioxidant activities                 | -                                           | -                             | -                                                                        | Riaz et al., 2018                                                          |
| 32. | Piperine  | Antioxidant, antitumor and bioavailability enhancer                      | -                                           | -                             | -                                                                        | Gorgani, Mohammadi, Najafpour, & Nikzad, 2017                              |
| 33. | Nicotiflorin | Antiglycation activity                                                   | -                                           | -                             | -                                                                        | Lal Shyaula et al., 2012                                                  |
| 34. | Gingerol  | Antioxidant, anti-tumor and anti-inflammatory properties                 | -                                           | -                             | -                                                                        | Mohd Yusof, 2016                                                          |
| 35. | Cannabidiol | Its relevance to epilepsy and other selected neuropsychiatric disorders | -                                           | -                             | -                                                                        | Devinsky et al., 2014                                                     |
| 36. | Aloesin   | Inhibitor of tyrosinase activity and up-regulates cyclin E-dependent kinase activity | -                                           | -                             | -                                                                        | Sánchez, González-Burgos, Iglesias, & Gómez-Serranillos, 2020              |
| No. | Compound          | Activities                                                                 | Source                                                                 |
|-----|-------------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------|
| 37. | Dehydroandrographolide | Anti-inflammation, anti-cancer, anti-bacterial, anti-virus and anti-hepatitis activity | Natural (H. Chen et al., 2014; J.-X. Chen et al., 2009)                |
| 38. | Aloenin           | Antiviral activity                                                          | Natural (Glatthaar-Saalmüller et al., 2015; Guo & Mei, 2016)          |
| 39. | Shogaol           | Decreased pain sensitivity and improved anxiety-like behavior, anti-inflammatory and anticancer | Natural (Mao et al., 2019; Shen et al., 2020)                         |
| 40. | Nimbin            | Anti-inflammatory, antipyretic, antifungal, antihistamine, antiseptic, antioxidant, anti-cancer and antiviral properties | Natural (Gorantla, Das, Mulani, Thulasiram, & Chinnathambi, 2019; WebPage, n.d.) |
| 41. | Lupeol            | Affects the molecular pathways of the nuclear factor kappa B(NFκB), cFLIP, Fas, Kras, phosphatidylinositol-3-kinase PI3K/Akt, and Wnt/β-catenin in a variety of cells. | Natural (Ruiz-Rodríguez et al., 2017)                                |
| 42. | Ursolic acid      | Anti-inflammatory, anti-oxidant, anti-apoptotic, and anti-carcinogenic effects | Natural (Seo et al., 2018)                                            |
**Table S3: In-Silico ADMET predictions of selected forty two compounds using SwissADME and PreADMET software.**

| Compound Name   | Molecular formula | MW     | HB A | HBD | n-rot b | TPSA (Å²) | Log P<sub>o/w</sub> | Log S | BBB | CYP 2D6 inhibitor | Lipinski | hERG_ inhibition | HIA (%) | PAIN S alert |
|-----------------|-------------------|--------|------|-----|---------|-----------|---------------------|-------|-----|-------------------|-----------|-----------------|---------|--------------|
| Umbralisib      | C_{33}H_{43}F_{3}N_{3}O_{3} | 601.79 | 11   | 5   | 6       | 104.04    | 3.26                | Soluble | No | No               | 1         | Ambiguous          | 85.54   | 0            |
| Baicalin        | C_{21}H_{16}O_{11} | 446.36 | 11   | 6   | 4       | 187.12    | 0.38                | Soluble | No | No               | 2         | Ambiguous          | 32.42   | 1            |
| Narirutin       | C_{27}H_{46}O_{14} | 594.65 | 14   | 9   | 6       | 228.22    | -2.53               | Soluble | No | No               | 3         | Ambiguous          | 3.55    | 0            |
| Bictegravir     | C_{21}H_{33}F_{3}N_{3}O_{5} | 465.51 | 11   | 5   | 4       | 108.66    | 0.28                | Soluble | No | No               | 0         | Ambiguous          | 66.6    | 0            |
| Scutellarin     | C_{21}H_{16}O_{12} | 480.50 | 12   | 9   | 4       | 209.76    | -2.46               | Soluble | No | No               | 2         | Ambiguous          | 2.913   | 0            |
| Complanatuside  | C_{28}H_{46}O_{16} | 640.67 | 16   | 10  | 8       | 257.68    | -3.02               | Soluble | No | No               | 3         | Ambiguous          | 1.42    | 0            |
| Sofosbuvir      | C_{22}H_{24}FN_{3}O_{3}P | 544.57 | 13   | 7   | 11      | 178.96    | -0.32               | Soluble | No | No               | 3         | Ambiguous          | 13.32   | 0            |
| Verdinexor      | C_{19}H_{32}F_{6}N_{6}O | 462.48 | 13   | 6   | 9       | 83.62     | 2.64                | Soluble | No | No               | 1         | Low Risk           | 66.14   | 0            |
| Pimobendan      | C_{19}H_{36}N_{4}O_{2} | 352.51 | 6    | 5   | 3       | 77.58     | 1.31                | Soluble | No | No               | 0         | Medium risk        | 75.57   | 0            |
| Eriocitrin      | C_{27}H_{46}O_{15} | 610.65 | 15   | 10  | 6       | 248.45    | -2.79               | Soluble | No | No               | 3         | Ambiguous          | 1.629   | 0            |
| Rutaecarpine    | C_{18}H_{31}N_{3}O | 305.46 | 4    | 3   | 0       | 47.53     | 1.80                | Soluble | Yes| No               | 0         | Medium risk        | 88.18   | 0            |
| Aprepitant      | C_{23}H_{37}F_{7}N_{4}O_{3} | 550.55 | 14   | 4   | 8       | 728.0     | 3.91                | Soluble | No | No               | 1         | Medium risk        | 85.34   | 0            |
| Amenamevir      | C_{29}H_{48}N_{4}O_{5}S | 5.473  | 9    | 7   | 8       | 154.78    | 1.58                | Soluble | No | No               | 2         | Ambiguous          | 60.79   | 0            |
| Amentoflavone | C<sub>30</sub>H<sub>18</sub>O<sub>10</sub> | 538.46 | 10 | 6 | 3 | 181.80 | 3.62 | Poorly soluble | No | No | 2 | Medium risk | 81.20 | 0 |
|--------------|---------------------------------|--------|----|----|----|---------|------|----------------|----|----|----|-------------|-------|---|
| Dolutegravir  | C<sub>20</sub>H<sub>35</sub>F<sub>2</sub>N<sub>5</sub>O<sub>5</sub> | 435.51 | 10 | 5 | 4 | 108.66 | 0.38 | Soluble | No | No | 0 | Ambiguous | 63.68 | 0 |
| Indigo       | C<sub>16</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub> | 280.41 | 4  | 4  | 1  | 64.52  | 1.21 | Soluble | No | No | 0 | Medium risk | 78.79 | 0 |
| Apigetrin    | C<sub>21</sub>H<sub>36</sub>O<sub>10</sub> | 448.50 | 10 | 7  | 4  | 169.30 | -1.00 | Soluble | No | No | 1 | Ambiguous | 13.79 | 0 |
| Oroxin B     | C<sub>27</sub>H<sub>46</sub>O<sub>15</sub> | 610.65 | 15 | 10 | 7  | 248.45 | -2.61 | Very Soluble | No | No | 3 | Ambiguous | 1.629 | 0 |
| Baloxavir    | C<sub>27</sub>H<sub>48</sub>F<sub>2</sub>N<sub>3</sub>O<sub>7</sub>S | 593.72 | 12 | 3  | 6  | 132.63 | 1.65 | Soluble | No | No | 1 | Ambiguous | 91.64 | 0 |
| GSK650394    | C<sub>23</sub>H<sub>44</sub>N<sub>2</sub>O<sub>2</sub> | 404.63 | 4  | 4  | 4  | 64.52  | 4.04 | Poorly Soluble | Yes | No | 1 | Medium risk | 87.32 | 0 |
| Dapivirine   | C<sub>20</sub>H<sub>41</sub>N<sub>5</sub> | 351.57 | 5  | 5  | 5  | 74.14  | 2.27 | Soluble | No | No | 0 | Medium risk | 78.7 | 0 |
| Homoorientin | C<sub>21</sub>H<sub>36</sub>O<sub>11</sub> | 464.50 | 11 | 9  | 3  | 200.53 | -2.55 | Soluble | No | No | 2 | Ambiguous | 3.44 | 0 |
| Luteoloside  | C<sub>21</sub>H<sub>36</sub>O<sub>11</sub> | 448.38 | 11 | 7  | 4  | 190.28 | 0.20 | Soluble | No | No | 2 | High risk | 25.16 | 1 |

Other natural compounds

| Berberine     | C<sub>20</sub>H<sub>18</sub>NO<sub>4</sub> | 336.4 | 4  | 0  | 2  | 40.8  | 2.53 | Moderately Soluble | yes | yes | 0 | Medium risk | 97.8 | 0 |
| Withanolide   | C<sub>23</sub>H<sub>38</sub>O<sub>6</sub> | 470.6 | 6  | 2  | 3  | 96.3  | 3.37 | Moderately Soluble | No | No | 0 | Low Risk | 94.7 | 0 |
| Withaferin A  | C<sub>23</sub>H<sub>38</sub>O<sub>6</sub> | 470.6 | 6  | 2  | 3  | 96.3  | 3.42 | Moderately Soluble | No | No | 0 | Low Risk | 94.7 | 0 |
| Compound          | Chemical Formula | MW  | Class       | pKa | Solubility       | Solubility2 | Medium Risk | Medium Risk2 |
|-------------------|------------------|-----|-------------|-----|------------------|-------------|-------------|--------------|
| Quercetin         | C_{15}H_{10}O_{7} | 302.2 | Soluble     | 1.23 | No               | No          | 0           | Medium risk  |
| Curcumin          | C_{21}H_{20}O_{6} | 368.4 | Moderately Soluble | 3.03 | No               | No          | 0           | Medium risk  |
| Sitosterol        | C_{29}H_{30}O_{6} | 414.7 | Poorly soluble | 7.24 | No               | No          | 1           | Low Risk     |
| Apigenin          | C_{15}H_{10}O_{5} | 270.2 | Moderately Soluble | 2.11 | Yes              | Yes         | 0           | Medium risk  |
| Astragalin        | C_{21}H_{20}O_{11} | 448.3 | Soluble     | -0.09 | No               | No          | 2           | High Risk    |
| Piperine          | C_{17}H_{19}NO_{3} | 285.3 | Soluble     | 3.04 | Yes              | Yes         | 0           | Medium risk  |
| Nicotiflorin      | C_{27}H_{30}O_{15} | 594.5 | Soluble     | -1.13 | No               | No          | 3           | High risk    |
| Gingerol          | C_{17}H_{26}O_{4} | 294.4 | Moderately Soluble | 3.13 | Yes              | Yes         | 0           | Low Risk     |
| Cannabidiol       | C_{21}H_{16}O_{2} | 314.4 | Moderately Soluble | 5.20 | Yes              | Yes         | 1           | Medium risk  |
| Aloesin           | C_{19}H_{22}O_{9} | 394.4 | Very Soluble | -0.30 | No               | No          | 0           | Low Risk     |
| Dehydroandrographide | C_{20}H_{28}O_{4} | 332.43 | Soluble     | 3.12 | Yes              | No          | 0           | Medium risk  |
| Aloenin           | C_{19}H_{22}O_{10} | 410.4 | Soluble     | 0.05 | No               | No          | 0           | Low Risk     |
| Shogaol           | C_{17}H_{24}O_{3} | 276.3 | Moderately Soluble | 3.76 | Yes              | Yes         | 0           | Medium risk  |
|            | C<sub>30</sub>H<sub>36</sub>O<sub>9</sub> | 540.6 | 9   | 0   | 8   | 118.3 | 3.20 | Moderately Soluble | No  | No  | 1 | Medium risk | 97.8 | 0 |
|------------|--------------------------------------|-------|-----|-----|-----|-------|------|-------------------|-----|-----|---|-------------|------|---|
| Nimbin     | C<sub>30</sub>H<sub>50</sub>O       | 426.7 | 1   | 1   | 1   | 20.2  | 7.28 | Poorly soluble    | No  | No  | 1 | Low Risk    | 100  | 0 |
| Lupeol     |                                      |       |     |     |     |       |      |                   |     |     |   |             |      |   |
| Ursolic acid| C<sub>30</sub>H<sub>48</sub>O<sub>3</sub> | 456.7 | 3   | 2   | 1   | 57.5  | 5.93 | Moderately Soluble| No  | No  | 1 | Low Risk    | 95.9 | 0 |

HBA hydrogen bond acceptor, ≤ 10; HBD hydrogen bond donor, ≤ 5; n-roth no. of rotatable bonds, ≤ 10; TPSA topological polar surface area, ≤ 130 Å<sup>2</sup>; Log Po/w octanol/water partition coefficient, −0.7 to +5.0; Log S, aqueous solubility scale: Insoluble < −10 < Poorly < −6 < Moderately < −4 < Soluble < −2 < Very Soluble < 0 < Highly soluble; BBB blood-brain barrier permeability, central nervous system toxicity; CYP2D6 inhibitor hepatotoxicity; Lipinski number of violations of Lipinski’s rule of five, maximum is 4; hERG inhibition risk; HIA human intestinal absorption, and PAINS (Pan-Assay Interference Compounds) alert.
Table S4: *In silico* toxicity prediction of selected forty two compounds using pkCSM software.

| Compound            | AMES toxicity Categorical (Yes/No) | Max. tolerated dose (human) Numeric (log mg/kg/day) | hERG I* inhibitor Categorical (Yes/No) | hERG II* inhibitor Categorical (Yes/No) | Oral rat acute toxicity (LD50*) Numeric (log mg/kg) | Oral rat chronic toxicity (LOAEL*) Numeric (log mg/kg bw/day) | Hepatotoxicity Categorical (Yes/No) | Skin sensitization Categorical (Yes/No) | T. pyriformis toxicity Numeric (log µg/L) | Fathead minnow toxicity Numeric (log mM) |
|---------------------|------------------------------------|---------------------------------------------------|----------------------------------------|------------------------------------------|------------------------------------------------|------------------------------------------------|-------------------------------------|-------------------------------------|--------------------------------|-------------------------------------|
| Umbralisib          | No                                 | -0.365                                            | No                                     | No                                       | 2.946                                           | 1.838                                           | No                                  | No                                  | 0.285                         | 3.601                               |
| Baicalin            | No                                 | 0.836                                             | No                                     | No                                       | 2.588                                           | 4.213                                           | No                                  | No                                  | 0.285                         | 2.02                                |
| Narirutin           | No                                 | 0.05                                              | No                                     | Yes                                      | 2.72                                            | 4.643                                           | No                                  | No                                  | 0.285                         | 7.961                               |
| Bictegravir         | No                                 | 0.742                                             | No                                     | No                                       | 2.019                                           | 4.253                                           | No                                  | No                                  | 0.285                         | 4.617                               |
| Scutellarin         | No                                 | 0.736                                             | No                                     | Yes                                      | 1.951                                           | 5.144                                           | No                                  | No                                  | 0.285                         | 8.134                               |
| Complanatuside      | No                                 | -0.236                                            | No                                     | Yes                                      | 2.869                                           | 4.682                                           | No                                  | No                                  | 0.285                         | 9.592                               |
| Sofosbuvir          | No                                 | 1.052                                             | No                                     | No                                       | 1.971                                           | 3.692                                           | No                                  | No                                  | 0.285                         | 6.119                               |
| Verdinexor          | No                                 | 0.508                                             | No                                     | Yes                                      | 2.904                                           | 2.221                                           | Yes                                 | No                                  | 0.285                         | 2.402                               |
| Pimobendan          | No                                 | -0.214                                            | No                                     | No                                       | 2.83                                            | 0.7                                             | Yes                                 | No                                  | 0.276                         | 2.865                               |
| Eriocitrin          | No                                 | 0.078                                             | No                                     | Yes                                      | 2.784                                           | 4.38                                            | No                                  | No                                  | 0.285                         | 9.395                               |
| Rutaecarpine        | No                                 | 0.1                                               | No                                     | No                                       | 2.494                                           | 1.323                                           | Yes                                 | No                                  | 0.284                         | 2.406                               |
| Aprepitant          | No                                 | 0.055                                             | No                                     | Yes                                      | 3.52                                            | 1.253                                           | Yes                                 | No                                  | 0.285                         | 4.678                               |
| Amenamevir          | No                                 | 0.389                                             | No                                     | No                                       | 2.236                                           | 2.569                                           | Yes                                 | No                                  | 0.285                         | 3.7                                 |
| Amentoflavone       | No                                 | 0.413                                             | No                                     | Yes                                      | 2.442                                           | 3.065                                           | No                                  | No                                  | 0.285                         | -0.801                              |
| Compound         | Value | Value | Value | Value | Value | Value | Value | Value |
|------------------|-------|-------|-------|-------|-------|-------|-------|-------|
| Dolutegravir     | No    | 0.579 | No    | No    | 1.884 | 4.023 | No    | 0.285 |
| Indigo           | No    | 0.991 | No    | No    | 2.304 | 2.209 | No    | 0.229 |
| Apigetrin        | No    | 0.248 | No    | No    | 2.644 | 3.776 | No    | 0.285 |
| OroxinB          | No    | -0.476| No    | Yes   | 2.92  | 6.116 | No    | 0.285 |
| Baloxavir        | No    | -0.568| No    | No    | 3.556 | 2.476 | Yes   | 0.285 |
| GSK650394        | No    | -1.285| No    | Yes   | 3.555 | 1.844 | Yes   | 0.289 |
| Dapivirine       | Yes   | 0.379 | No    | Yes   | 2.599 | 0.704 | Yes   | 0.266 |
| Homoorientin     | No    | 0.417 | No    | No    | 2.567 | 4.805 | No    | 0.285 |
| Luteoloside      | No    | 0.724 | No    | Yes   | 2.689 | 4.425 | No    | 0.285 |
| **Other natural compounds** | | | | | | | | |
| Berberine        | No    | -0.043| No    | Yes   | 3.377 | 1.388 | yes   | 0.3   |
| Withanolide      | No    | -0.224| No    | No    | 2.743 | 2.229 | No    | 0.294 |
| Withaferin A     | No    | -0.192| No    | No    | 2.836 | 2.083 | No    | 0.294 |
| Quercetin        | No    | 1     | No    | No    | 2.288 | 2.996 | No    | 0.303 |
| Curcumin         | No    | 0.697 | No    | No    | 2.132 | 3.499 | No    | 0.575 |
| Sitosterol       | No    | -0.798| No    | Yes   | 3.892 | 1.007 | No    | 0.424 |
| Apigenin         | No    | 0.437 | No    | Yes   | 2.408 | 1.737 | No    | 0.464 |
| Astragalin       | No    | 0.821 | No    | Yes   | 2.959 | 2.098 | No    | 0.285 |
| Piperine         | No    | -0.311| No    | No    | 2.867 | 1.499 | yes   | 1.868 |
|                | hERG* | LD50* | LOAEL* |    |    |    |    |    |    |
|----------------|-------|-------|--------|----|----|----|----|----|----|
| Nicotiflorin   | No    | 0.73  | No     | Yes| 2.763 | 3.677 | No | No | 0.285 | 4.568 |
| Gingerol       | No    | 0.355 | No     | Yes| 2.272 | 2.417 | No | No | 0.86   | 0.035  |
| Cannabidiol    | No    | -0.798| No     | Yes| 3.892 | 1.007 | No | No | 0.424  | -1.255 |
| Aloesin        | No    | 0.898 | No     | No | 3.146 | 2.881 | Yes| No | 0.288  | 2.91   |
| Dehydroandrographolide | No   | -0.792| No     | No | 3.204 | 1.64  | No | No | 0.393  | 0.646  |
| Aloenin        | No    | 0.73  | No     | No | 3.154 | 2.492 | Yes| No | 0.287  | 3.134  |
| Shogaol        | No    | 0.679 | No     | No | 2.181 | 2.542 | No | Yes| 1.446  | -0.191 |
| Nimbin         | No    | -0.048| No     | No | 2.293 | 1.771 | No | No | 0.288  | 2.07   |
| Lupeol         | No    | -0.193| No     | No | 4.145 | 1.708 | No | No | 0.317  | -1.31  |
| Ursolic acid   | No    | 1.161 | No     | No | 3.115 | 2.08  | yes| No | 0.288  | -0.368 |

hERG*: human Ether-à-go-go-Related Gene; LD50*: lethal dose of 50%; LOAEL*: lowest observed adverse effect level.
Figure S4: The predictions of selected twelve plant based natural Compounds human intestinal absorption (HIA) and brain permeation (BBB) determined using the tPSA/WLogP-based graphical BOILED-Egg method predicted by online SwissADME (https://www.swissadme.ch) web tool. Each compound corresponds to a small red, blue and black circle. The grey region is the physicochemical space of compounds predicted to exhibit high intestinal absorption. The yellow part is the physicochemical space of compounds predicted to permeate the brain. Abbreviation: topological polar surface area (tPSA). As shown in Figure, the egg-shaped yolk space for highly probable BBB permeation and the white space for highly probable HIA absorption. The blue colour indicates effluxed by P-glycoprotein (PGP+), whereas the red colour indicates nonsubstrate of P-gp (PGP-).
Figure S5: Radar plot for oral bioavailability of the twelve-plant based natural compounds predicted by online SwissADME (https://www.swissadme.ch) web tool. Pink area represents the range of optimal values. The coloured zone is a suitable physicochemical space for oral bioavailability. Any deviation represents a suboptimal physicochemical property for oral bioavailability. LIPO (Lipophilicity): $-0.7 < \text{XLOGP3} < 5.0$; SIZE: 150 g/mol < MW < 500 g/mol; POLAR (Polarity): 20 Å² < TPSA < 130 Å²; INSOLU (Insolubility): 0 < Log S (ESOL) < 6; INSATU (Insaturation): 0.25 < Fraction Csp3 < 1; FLEX (Flexibility): 0 < Num. rotatable bonds < 9.
**Figure S6**: The Pie-chart of top-15 of target predicted for twelve selected natural compounds predicted by online SwissTargetPrediction (http://www.swisstargetprediction.ch) web tool.

**Target prediction analysis** (Figure S6 and Table S5):
The targets of Narirutin were predicted to be the family AG protein-coupled receptors (33.3%), Other cytosolic protein (26.7%), secreted proteins (20%), enzymes (13.3%), and kinase (6.7%), with a probability of below 1%. In Scutellarin, there was a potential target with family AG protein-coupled receptors (40%), Other cytosolic protein (20%), and secreted proteins (20%), enzymes (13.3%), and kinase 96.75) with a probability of below 1%. The targets of Complanatuside were predicted to be the family AG protein-coupled receptors (46.7%), secreted proteins (20%), kinase (6.7%), enzymes and other cytosolic protein (13.3) with a probability of less than 1%. In Eriocitrin, there was a potential target with the family AG protein-coupled receptors (53.3%), secreted proteins (20%), enzymes (13.3%), other cytosolic protein and cytochrome P450 (6.7%) with a probability of below 1% each. Likewise, Oroxin B showed a potential target of the family AG protein-coupled receptors (33.3%), other cytosolic protein (26.7%), secreted proteins (20%), enzyme (13.3%) and kinase (6.7%), with a probability of below 1%. The targets of Homoorientin were predicted to be proteases (40%), secreted proteins and enzymes (20%), the family AG protein-coupled receptors, primary active transporters, and Electrochemical transporter (6.7%) with a probability of less than 1%. 
Table S5: The potential target of twelve selected plant based natural compounds in the human proteome, predicted through Swiss target prediction.

| Baicalin | Common name | Uniprot ID | ChEMBL ID | Target Class | Probability* | Known actives (3D/2D) |
|----------|-------------|------------|-----------|--------------|--------------|-----------------------|
| Aldose reductase (by homology) | AKR1B1 | P15121 | CHEMBL1900 | Enzyme | 0.15634 | 7 / 69 Â Â Â Â Â |
| Adenosine A1 receptor (by homology) | ADORA1 | P30542 | CHEMBL226 | Family A G protein-coupled receptor | 0.123138 | 38 / 15 Â Â Â Â Â |
| TNF-alpha | TNF | P01375 | CHEMBL1825 | Secreted protein | 0.114839 | 0 / 3 Â Â Â Â Â |
| Interleukin-2 | IL2 | P60568 | CHEMBL5880 | Secreted protein | 0.114839 | 0 / 4 Â Â Â Â Â |
| Xanthine dehydrogenase | XDH | P47989 | CHEMBL1929 | Oxidoreductase | 0.106543 | 0 / 19 Â Â Â Â Â |
| Cylooxygenase-2 Ribosomal protein S6 kinase alpha 3 | PTGS2 | P35354 | CHEMBL230 | Oxidoreductase | 0.106543 | 0 / 5 Â Â Â Â Â |
| Epidermal growth factor receptor erbB1 | EGFR | P00533 | CHEMBL203 | Kinase | 0.106543 | 0 / 19 Â Â Â Â Â |
| Acetylcholinesterase | ACHE | P22303 | CHEMBL220 | Hydrolase | 0.106543 | 0 / 28 Â Â Â Â Â |
| Quinone reductase 2 | NQO2 | P16083 | CHEMBL3959 | Enzyme | 0.106543 | 0 / 1 Â Â Â Â Â |
| Neuromedin-U receptor 2 | NMUR2 | Q9GZQ4 | CHEMBL1075144 | Protein-coupled receptor | 0.106543 | 0 / 1 Â Â Â Â Â |
| Alpha-2a adrenergic receptor | ADRA2A | P08913 | CHEMBL1867 | Family A G protein-coupled receptor | 0.106543 | 0 / 1 Â Â Â Â Â |
| Adrenergic receptor alpha-2 | ADRA2C | P18825 | CHEMBL1916 | Family A G protein-coupled receptor | 0.106543 | 0 / 2 Â Â Â Â Â |
| NADPH oxidase 4 | NOX4 | Q9NPH5 | CHEMBL1250375 | Enzyme | 0.106543 | 0 / 7 Â Â Â Â Â |
| Aldehyde dehydrogenase | ALDH2 | P05091 | CHEMBL1935 | Oxidoreductase | 0.106543 | 0 / 24 Â Â Â Â Â |

| Narirutin | Common name | Uniprot ID | ChEMBL ID | Target Class | Probability* | Known actives (3D/2D) |
|-----------|-------------|------------|-----------|--------------|--------------|-----------------------|
| Basic fibroblast growth factor | FGF2 | P09038 | CHEMBL3107 | Secreted protein | 0.243785537 | 3 / 3 Â Â Â Â Â |
| Scutellarin | Common name | Uniprot ID | ChEMBL ID | Target Class | Probability* | Known actives (3D/2D) |
|-------------|-------------|------------|-----------|--------------|--------------|-----------------------|
| Heat shock protein HSP 90-alpha | HSP90AA1 | P07900 | CHEMBL3880 | Other cytosolic protein | 0.127881258 | 12 / 3Å Å Å Å Å Å |
| Vascular endothelial growth factor A | VEGFA | P15692 | CHEMBL1783 | Secreted protein | 0.110041254 | 2 / 4Å Å Å Å Å Å |
| Acidic fibroblast growth factor | FGF1 | P05230 | CHEMBL2120 | Secreted protein | 0.110041254 | 1 / 7Å Å Å Å Å Å |
| Heparanase | HPSE | Q9Y251 | CHEMBL3921 | Enzyme | 0.110041254 | 1 / 5Å Å Å Å Å Å |
| Vascular endothelial growth factor A | VEGFA | P15692 | CHEMBL1783 | Secreted protein | 0.110041254 | 2 / 4Å Å Å Å Å Å |
| Acidic fibroblast growth factor | FGF1 | P05230 | CHEMBL2120 | Secreted protein | 0.110041254 | 1 / 7Å Å Å Å Å Å |
| Heparanase | HPSE | Q9Y251 | CHEMBL3921 | Enzyme | 0.110041254 | 1 / 5Å Å Å Å Å Å |
| Gamma-secretase | APH1B | Q8WW43 | CHEMBL2094135 | Protease | 0.101086931 | 0 / 14Å Å Å Å Å Å |
| Galectin-3 | LGALS3 | P17931 | CHEMBL4531 | Other cytosolic protein | 0.074392272 | 9 / 4Å Å Å Å Å Å |
| Cyclin-dependent kinase 1 | CDK1 | P06493 | CHEMBL308 | Kinase | 0.074392272 | 5 / 1Å Å Å Å Å Å |
| Galectin-4 | LGALS4 | P56470 | CHEMBL1671608 | Other cytosolic protein | 0.074392272 | 2 / 3Å Å Å Å Å Å |
| Galectin-8 | LGALS8 | O00214 | CHEMBL5475 | Other cytosolic protein | 0.074392272 | 2 / 3Å Å Å Å Å Å |
| Serotonin 2b (5-HT2b) receptor | HTR2B | P41595 | CHEMBL1833 | Family A G protein-coupled receptor | 0.074392272 | 0 / 1Å Å Å Å Å Å |
| Alpha-2a adrenergic receptor | ADRA2A | P08913 | CHEMBL1867 | Family A G protein-coupled receptor | 0.074392272 | 0 / 1Å Å Å Å Å Å |
| Adrenergic receptor alpha-2 | ADRA2C | P18825 | CHEMBL1916 | Family A G protein-coupled receptor | 0.074392272 | 0 / 1Å Å Å Å Å Å |
| Alpha-2b adrenergic receptor | ADRA2B | P18089 | CHEMBL1942 | Family A G protein-coupled receptor | 0.074392272 | 0 / 1Å Å Å Å Å Å |
| Protein Name                        | Accession | CHEMBL   | Function               | ProtScore | PDB Code 1 | PDB Code 2 |
|------------------------------------|-----------|----------|------------------------|-----------|------------|------------|
| Vascular endothelial growth factor A | VEGFA     | P15692   | CHEMBL1783 Secreted protein | 0.192799869 | 0 / 2Â Â Â Â Â Â |
|                                    | PSEN2     | P49810   | CHEMBL1783 Secreted protein | 0.192799869 | 0 / 2Â Â Â Â Â Â |
|                                    | PSENEN    | Q9NZ42   | CHEMBL1783 Secreted protein | 0.192799869 | 0 / 2Â Â Â Â Â Â |
|                                    | NCSTN     | Q92542   | CHEMBL1783 Secreted protein | 0.192799869 | 0 / 2Â Â Â Â Â Â |
|                                    | APH1A     | Q96B13   | CHEMBL1783 Secreted protein | 0.192799869 | 0 / 2Â Â Â Â Â Â |
|                                    | PSEN1     | P49768   | CHEMBL1783 Secreted protein | 0.192799869 | 0 / 2Â Â Â Â Â Â |
| Gamma-secretase                    | APH1B     | Q8WW43   | CHEMBL2094135 Protease | 0.192799869 | 0 / 12Â Â Â Â Â Â |
| Acidic fibroblast growth factor    | FGF1      | P05230   | CHEMBL2120 Secreted protein | 0.192799869 | 0 / 7Â Â Â Â Â Â |
| Basic fibroblast growth factor     | FGF2      | P09038   | CHEMBL3107 Secreted protein | 0.192799869 | 0 / 4Â Â Â Â Â Â |
| Heparanase                         | HPSE      | Q9Y251   | CHEMBL3921 Enzyme | 0.192799869 | 0 / 5Â Â Â Â Â Â |
| Heat shock protein HSP 90-alpha    | HSP90AA1  | P07900   | CHEMBL3880 Other cytosolic protein | 0.100634432 | 1 / 3Â Â Â Â Â Â |
| Galectin-4                         | LGALS4    | P56470   | CHEMBL1671608 Other cytosolic protein | 0.100634432 | 0 / 3Â Â Â Â Â Â |
| Galectin-8                         | LGALS8    | O00214   | CHEMBL5475 Other cytosolic protein | 0.100634432 | 0 / 3Â Â Â Â Â Â |
| Cyclin-dependent kinase 1          | CDK1      | P06493   | CHEMBL308 Kinase | 0.100634432 | 0 / 1Â Â Â Â Â Â |
| Serotonin 2b (5-HT2b) receptor     | HTR2B     | P41595   | CHEMBL1833 Family A G protein-coupled receptor | 0.100634432 | 0 / 1Â Â Â Â Â Â |
| Alpha-2a adrenergic receptor       | ADRA2A    | P08913   | CHEMBL1867 Family A G protein-coupled receptor | 0.100634432 | 0 / 1Â Â Â Â Â Â |
| Adrenergic receptor alpha-2        | ADRA2C    | P18825   | CHEMBL1916 Family A G protein-coupled receptor | 0.100634432 | 0 / 1Â Â Â Â Â Â |
| Alpha-2b adrenergic receptor       | ADRA2B    | P18089   | CHEMBL1942 Family A G protein-coupled receptor | 0.100634432 | 0 / 1Â Â Â Â Â Â |
| Dopamine D1 receptor               | DRD1      | P21728   | CHEMBL2056 Family A G protein-coupled receptor | 0.100634432 | 0 / 1Â Â Â Â Â Â |
| Dopamine D2 receptor               | DRD2      | P14416   | CHEMBL217 Family A G protein-coupled receptor | 0.100634432 | 0 / 1Â Â Â Â Â Â |
| Complanatuside                  | Common name                        | Uniprot ID | ChEMBL ID   | Target Class | Probability* | Known actives (3D/2D) |
|--------------------------------|------------------------------------|------------|-------------|--------------|--------------|-----------------------|
| Basic fibroblast growth factor | FGF2                               | P09038     | CHEMBL3107  | Secreted protein | 0.388188  | 4 / 3 Â Â Â Â Â Â |
| Vascular endothelial growth factor A | VEGFA                             | P15692     | CHEMBL1783  | Secreted protein | 0.207529  | 1 / 4 Â Â Â Â Â Â |
| Acidic fibroblast growth factor | FGF1                               | P05230     | CHEMBL2120  | Secreted protein | 0.207529  | 1 / 7 Â Â Â Â Â Â |
| Heparanase                      | HPSE                               | Q9Y251     | CHEMBL3921  | Enzyme        | 0.207529   | 1 / 5 Â Â Â Â Â Â |
|                                | PSEN2                              | P49810     |             |              |             |                      |
|                                | PSENE                              | Q9NZ42     |             |              |             |                      |
|                                | NCSTN                              | Q92542     |             |              |             |                      |
|                                | APH1A                              | Q96B13     |             |              |             |                      |
|                                | PSEN1                              | P49768     |             |              |             |                      |
| Gamma-secretase                | HSP90AA1                           | P07900     | CHEMBL3880  | Other cytosolic protein | 0.093576  | 7 / 3 Â Â Â Â Â Â |
| Heat shock protein HSP 90-alpha| LGALS3                             | P17931     | CHEMBL4531  | Other cytosolic protein | 0.084066  | 5 / 4 Â Â Â Â Â Â |
| Galectin-3                     | CDK1                               | P06493     | CHEMBL308   | Kinase        | 0.084066   | 3 / 1 Â Â Â Â Â Â |
| Cyclin-dependent kinase 1      | HTR2B                              | P41595     | CHEMBL1833  | Family A G protein-coupled receptor | 0.074565  | 0 / 1 Â Â Â Â Â Â |
| Serotonin 2b (5-HT2b) receptor | ADRA2A                             | P08913     | CHEMBL1867  | Family A G protein-coupled receptor | 0.074565  | 0 / 1 Â Â Â Â Â Â |
| Alpha-2a adrenergic receptor    | ADRA2C                             | P18825     | CHEMBL1916  | Family A G protein-coupled receptor | 0.074565  | 0 / 1 Â Â Â Â Â Â |
| Adrenergic receptor alpha-2     | ADRA2B                             | P18089     | CHEMBL1942  | Family A G protein-coupled receptor | 0.074565  | 0 / 1 Â Â Â Â Â Â |
| Alpha-2b adrenergic receptor    | DRD1                               | P21728     | CHEMBL2056  | Family A G protein-coupled receptor | 0.074565  | 0 / 1 Â Â Â Â Â Â |
| Dopamine D1 receptor            | ADRA1D                             | P25100     | CHEMBL223   | Family A G protein-coupled receptor | 0.074565  | 0 / 1 Â Â Â Â Â Â |
| Erictin | Common name | Uniprot ID | ChEMBL ID | Target Class | Probability* | Known actives (3D/2D) |
|---------|-------------|------------|-----------|--------------|--------------|----------------------|
| Vascular endothelial growth factor A | VEGFA | P15692 | CHEMBL1783 | Secreted protein | 0.325352 | 2 / 4 Â Â Â Â Â |
| Acidic fibroblast growth factor | FGF1 | P05230 | CHEMBL2120 | Secreted protein | 0.325352 | 2 / 7 Â Â Â Â Â |
| Basic fibroblast growth factor | FGF2 | P09038 | CHEMBL3107 | Secreted protein | 0.325352 | 5 / 3 Â Â Â Â Â |
| Heparanase | HPSE | Q9Y251 | CHEMBL3921 | Enzyme | 0.325352 | 2 / 5 Â Â Â Â Â |
| Gamma-secretase | APH1B | Q8WW43 | CHEMBL2094135 | Protease | 0.109233 | 0 / 14 Â Â Â Â Â |
| Heat shock protein HSP 90-alpha | HSP90AA1 | P07900 | CHEMBL3880 | Other cytosolic protein | 0.082222 | 6 / 3 Â Â Â Â Â |
| Serotonin 2b (5-HT2b) receptor | HTR2B | P41595 | CHEMBL1833 | Family A G protein-coupled receptor | 0.082222 | 0 / 1 Â Â Â Â Â |
| Alpha-2a adrenergic receptor | ADRA2A | P08913 | CHEMBL1867 | Family A G protein-coupled receptor | 0.082222 | 0 / 1 Â Â Â Â Â |
| Adrenergic receptor alpha-2 | ADRA2C | P18825 | CHEMBL1916 | Family A G protein-coupled receptor | 0.082222 | 0 / 1 Â Â Â Â Â |
| Alpha-2b adrenergic receptor | ADRA2B | P18089 | CHEMBL1942 | Family A G protein-coupled receptor | 0.082222 | 0 / 1 Â Â Â Â Â |
| Dopamine D1 receptor | DRD1 | P21728 | CHEMBL2056 | Family A G protein-coupled receptor | 0.082222 | 0 / 1 Â Â Â Â Â |
| Serotonin 2a (5-HT2a) receptor | HTR2A | P28223 | CHEMBL224 | Family A G protein-coupled receptor | 0.082222 | 0 / 1 Â Â Â Â Â |
| Common name                                      | Uniprot ID | ChEMBL ID | Target Class                              | Probability* | Known actives (3D/2D) | Probability* | Known actives (3D/2D) |
|-------------------------------------------------|------------|-----------|-------------------------------------------|--------------|------------------------|--------------|------------------------|
| Serotonin 2c (5-HT2c) receptor                   | HTR2C      | P28335    | CHEMBL225                                 | Family A G protein-coupled receptor | 0.082222     | 0 / 1                 |                        |
| Dopamine D3 receptor                             | DRD3       | P35462    | CHEMBL234                                 | Family A G protein-coupled receptor | 0.082222     | 0 / 1                 |                        |
| Cytochrome P450 2D6                              | CYP2D6     | P10635    | CHEMBL289                                 | Cytochrome P450 | 0.082222     | 0 / 1                 |                        |
| Rutaecarpine                                    |            |           |                                           |              |                        |              |                        |
| Muscarinic acetylcholine receptor M4             | CHRM4      | P08173    | CHEMBL1821                                | Family A G protein-coupled receptor | 0.111502     | 49 / 0                |                         |
| Muscarinic acetylcholine receptor M2             | CHRM2      | P08172    | CHEMBL211                                 | Family A G protein-coupled receptor | 0.111502     | 182 / 0               |                         |
| Muscarinic acetylcholine receptor M1             | CHRM1      | P11229    | CHEMBL216                                 | Family A G protein-coupled receptor | 0.111502     | 183 / 0               |                         |
| Muscarinic acetylcholine receptor M3             | CHRM3      | P20309    | CHEMBL245                                 | Family A G protein-coupled receptor | 0.111502     | 171 / 0               |                         |
| Dopamine D4 receptor                             | DRD4       | P21917    | CHEMBL219                                 | Family A G protein-coupled receptor | 0.111502     | 164 / 0               |                         |
| Vesicular acetylcholine transporter              | SLC18A3    | Q16572    | CHEMBL4767                                | Electrochemical transporter Family A G protein-coupled receptor | 0.111502     | 168 / 0               |                         |
| Muscarinic acetylcholine receptor M5             | CHRM5      | P08912    | CHEMBL2035                                | Voltage-gated ion channel Electrochemical transporter | 0.111502     | 41 / 0                |                         |
| HERG                                            | KCNH2      | Q12809    | CHEMBL240                                 | Electrochemical transporter | 0.111502     | 356 / 0               |                         |
| Norepinephrine transporter                       | SLC6A2     | P23975    | CHEMBL222                                 | Electrochemical transporter | 0.111502     | 514 / 0               |                         |
| Serotonin transporter                            | SLC6A4     | P31645    | CHEMBL228                                 | Electrochemical transporter | 0.111502     | 895 / 0               |                         |
| Dopamine transporter                             | SLC6A3     | Q01959    | CHEMBL238                                 | Electrochemical transporter | 0.111502     | 627 / 0               |                         |
| Aprepitant                                      | Common name                  | Uniprot ID | ChEMBL ID   | Target Class                  | Probability* | Known actives (3D/2D) |
|------------------------------------------------|------------------------------|------------|-------------|------------------------------|--------------|-----------------------|
| Methionine aminopeptidase 2                    | METAP2                       | P50579     | CHEMBL3922  | Protease Family A G protein-coupled receptor | 0.111502     | 56 / 0Å Å Å Å Å Å     |
| Dopamine D3 receptor                            | DRD3                         | P35462     | CHEMBL234   | Kinase Primary active transporter | 0.111502     | 293 / 0Å Å Å Å Å Å   |
| Dual specificity mitogen-activated protein kinase 1 | MAP2K1                       | Q02750     | CHEMBL3587  | Kinase                        | 0.111502     | 112 / 0Å Å Å Å Å Å  |
| P-glycoprotein 1                                | ABCB1                        | P08183     | CHEMBL4302  | Protease                      | 0.111502     | 181 / 0Å Å Å Å Å Å |
| Pyruvate dehydrogenase kinase isoform 2         | PDK2                         | Q15119     | CHEMBL3861  | Kinase Voltage-gated ion channel | 0.125687     | 170 / 0Å Å Å Å Å Å |
| Sodium channel protein type IX alpha subunit    | SCN9A                        | Q15858     | CHEMBL4296  | Voltage-gated ion channel     | 0.125687     | 400 / 0Å Å Å Å Å Å |
| Protein-tyrosine phosphatase 1B                 | PTPN1                        | P18031     | CHEMBL335   | Phosphatase                   | 0.125687     | 23 / 0Å Å Å Å Å Å  |
| T-cell protein-tyrosine phosphatase             | PTPN2                        | P17706     | CHEMBL3807  | Phosphatase                   | 0.125687     | 13 / 0Å Å Å Å Å Å  |
| Matrix metalloproteinase 12                     | MMP12                        | P39900     | CHEMBL4393  | Protease                      | 0.125687     | 2 / 0Å Å Å Å Å Å  |
| Caspase-8                                       | CASP8                        | P14790     | CHEMBL3776  | Protease                      | 0.125687     | 4 / 0Å Å Å Å Å Å  |
| Caspase-1                                       | CASP1                        | P29466     | CHEMBL4801  | Protease                      | 0.125687     | 5 / 0Å Å Å Å Å Å  |
| PI3-kinase p110-delta subunit                   | PIK3CD                       | O00329     | CHEMBL3130  | Enzyme                        | 0.125687     | 46 / 0Å Å Å Å Å Å |
| PI3-kinase p110-beta subunit                   | PIK3CB                       | P42338     | CHEMBL3145  | Enzyme                        | 0.125687     | 48 / 0Å Å Å Å Å Å |
| Protein kinase C epsilon                        | PRKCE                        | Q02156     | CHEMBL3582  | Kinase                        | 0.125687     | 5 / 0Å Å Å Å Å Å  |
| PI3-kinase p110-gamma subunit                  | PIK3CG                       | P48736     | CHEMBL3267  | Enzyme                        | 0.125687     | 31 / 0Å Å Å Å Å Å |
| PI3-kinase p110-alpha subunit                  | PIK3CA                       | P42336     | CHEMBL4005  | Enzyme Family A G protein-coupled receptor | 0.125687     | 68 / 0Å Å Å Å Å Å |
| Neurokinin 1 receptor                           | TACR1                        | P25103     | CHEMBL249   | Kinase                        | 0.125687     | 303 / 0Å Å Å Å Å Å |
| Nerve growth factor receptor Trk-A              | NTRK1                        | P04629     | CHEMBL2815  | Kinase                        | 0.125687     | 24 / 0Å Å Å Å Å Å |
| Target Name                                                                 | Common name | Uniprot ID | ChEMBL ID      | Target Class                      | Probability* | Known actives (3D/2D) |
|----------------------------------------------------------------------------|-------------|------------|----------------|-----------------------------------|--------------|-----------------------|
| Beta-secretase 1                                                           | BACE1       | P56817     | CHEMBL4822     | Protease                          | 0.125687     | 46 / 0 Â Â Â Â Â Â |
| Amentoflavone                                                              | VCP         | P55072     | CHEMBL1075145  | Primary active transporter         | 1            | 1 / 1 Â Â Â Â Â Â |
| Placenta growth factor                                                    | PGF         | P49763     | CHEMBL1697671  | Unclassified protein              | 1            | 1 / 1 Â Â Â Â Â Â |
| Vascular endothelial growth factor A                                      | VEGFA       | P15692     | CHEMBL1783     | Secreted protein                  | 1            | 1 / 1 Â Â Â Â Â Â |
| GABA-A receptor; alpha-1/beta-2/gamma-2                                   | GABRA1      | P14867     |                |                                   |              |                      |
| GABRB2                                                                    | P47870      |            |                |                                   |              |                      |
| GABRG2                                                                    | P18507      |            |                |                                   |              |                      |
| GABA-A receptor; alpha-1/beta-2/gamma-2                                   | HTR2C       | P28335     | CHEMBL225      | Ligand-gated ion channel          | 1            | 1 / 1 Â Â Â Â Â Â |
| Vascular endothelial growth factor A                                      | VEGFA       | P15692     | CHEMBL1783     | Secreted protein                  | 1            | 1 / 1 Â Â Â Â Â Â |
| Dopamine D3 receptor                                                       | DRD3        | P35462     | CHEMBL234      | Family A G protein-coupled receptor | 1            | 1 / 1 Â Â Â Â Â Â |
| Delta opioid receptor                                                      | OPRD1       | P41143     | CHEMBL236      | Family A G protein-coupled receptor | 1            | 2 / 5 Â Â Â Â Â Â |
| Protein-tyrosine phosphatase 1B                                            | PTPN1       | P18031     | CHEMBL335      | Phosphatase                        | 1            | 6 / 18 Â Â Â Â Â Â |
| Beta-secretase 1                                                           | BACE1       | P56817     | CHEMBL4822     | Protease                          | 1            | 10 / 17 Â Â Â Â Â Â |
| Cyclin-dependent kinase 5/CDK5 activator 1                                | CDK5R1      | Q15078     | CHEMBL1187942  | Kinase                            | 0.086886     | 1 / 17 Â Â Â Â Â Â |
| NEDD8-activating enzyme E1 regulatory subunit                             | NAE1        | Q13564     | CHEMBL2016431  | Unclassified protein              | 0            | 0 / 1 Â Â Â Â Â Â |
| NADPH oxidase 4                                                            | NOX4        | Q9NPH5     | CHEMBL1250375  | Enzyme                            | 0            | 0 / 7 Â Â Â Â Â Â |
| Aldose reductase (by homology)                                             | AKR1B1      | P15121     | CHEMBL1900     | Enzyme                            | 0            | 0 / 61 Â Â Â Â Â Â |
| Monoamine oxidase A                                                        | MAOA        | P21397     | CHEMBL1951     | Oxidoreductase                     | 0            | 0 / 6 Â Â Â Â Â Â |
| Tyrosine-protein kinase receptor FLT3                                      | FLT3        | P36888     | CHEMBL1974     | Kinase                            | 0            | 0 / 7 Â Â Â Â Â Â |

| Apigetrin                                                                 | Common name | Uniprot ID | ChEMBL ID      | Target Class                      | Probability* | Known actives (3D/2D) |
|----------------------------------------------------------------------------|-------------|------------|----------------|-----------------------------------|--------------|-----------------------|
|                                                                             |             |            |                |                                   |              |                      |

**Notes:**
- The table lists various targets along with their identification numbers and corresponding data points.
- The columns include Common name, Uniprot ID, ChEMBL ID, Target Class, Probability, and Known actives (3D/2D).
- The probability values are marked as 0 or 1, indicating whether the target is known to have known actives in 3D or 2D format.
| Protein Name                        | Accession | PDB ID | Function          | IC50   | Ki (nM) |
|------------------------------------|-----------|--------|-------------------|--------|---------|
| Vascular endothelial growth factor A | CHEMBL1783 | P15692 | Secreted protein  | 0.191272 | 0 / 2  |
| Gamma-secretase                    | CHEMBL2094135 | P49810 | Protease          | 0.191272 | 0 / 3  |
| Acidic fibroblast growth factor    | CHEMBL2120 | P49810 | Secreted protein  | 0.191272 | 0 / 4  |
| Basic fibroblast growth factor     | CHEMBL3107 | P49810 | Secreted protein  | 0.191272 | 0 / 5  |
| Heparanase                         | CHEMBL3921 | P49810 | Enzyme            | 0.126929 | 0 / 6  |
| Heat shock protein HSP 90-alpha    | CHEMBL3880 | P49810 | Other cytosolic protein | 0.118883 | 0 / 7  |
| Serotonin 2b (5-HT2b) receptor     | CHEMBL1833 | P49810 | Family A G protein-coupled receptor | 0.118883 | 0 / 8  |
| Alpha-2a adrenergic receptor       | CHEMBL1867 | P49810 | Family A G protein-coupled receptor | 0.118883 | 0 / 9  |
| Adrenergic receptor alpha-2        | CHEMBL1916 | P49810 | Family A G protein-coupled receptor | 0.118883 | 0 / 10 |
| Alpha-2b adrenergic receptor       | CHEMBL1942 | P49810 | Family A G protein-coupled receptor | 0.118883 | 0 / 11 |
| Dopamine D1 receptor               | CHEMBL2056 | P49810 | Family A G protein-coupled receptor | 0.118883 | 0 / 12 |
| Alpha-1d adrenergic receptor       | CHEMBL223  | P49810 | Family A G protein-coupled receptor | 0.118883 | 0 / 13 |
| Serotonin 2a (5-HT2a) receptor     | CHEMBL224  | P49810 | Family A G protein-coupled receptor | 0.118883 | 0 / 14 |
| Common name                              | Uniprot ID | ChEMBL ID | Target Class      | Probability* | Known actives (3D/2D) |
|------------------------------------------|------------|-----------|-------------------|--------------|-----------------------|
| Basic fibroblast growth factor           | FGF2       | P09038    | CHEMBL3107        | 0.199274     | 4 / 3              |
| Vascular endothelial growth factor A     | VEGFA      | P15692    | CHEMBL1783        | 0.109233     | 1 / 4              |
| Acidic fibroblast growth factor          | FGF1       | P05230    | CHEMBL2120        | 0.109233     | 1 / 7              |
| Heparanase                               | HPSE       | Q9Y251    | CHEMBL3921        | 0.109233     | 1 / 5              |
|                                         | PSEN2      | P49810    |                   |              |                      |
|                                         | PSENEN     | Q9NZ42    |                   |              |                      |
|                                         | NCSTN      | Q92542    |                   |              |                      |
|                                         | APH1A      | Q96B13    |                   |              |                      |
|                                         | PSEN1      | P49768    |                   |              |                      |
|                                         | APH1B      | Q8WW43    |                   |              |                      |
| Gamma-secretase                          | HSP90AA1   | P07900    | CHEMBL3880        | 0.091209     | 8 / 3              |
| Heat shock protein HSP 90-alpha          |            |           |                   |              |                      |
| Galectin-4                               | LGALS4     | P56470    | CHEMBL1671608     | 0.091209     | 2 / 3              |
| Galectin-3                               | LGALS3     | P17931    | CHEMBL4531        | 0.091209     | 10 / 4             |
| Galectin-8                               | LGALS8     | O00214    | CHEMBL5475        | 0.091209     | 2 / 3              |
| Cyclin-dependent kinase 1                | CDK1       | P06493    | CHEMBL308         | 0.082222     | 3 / 1              |
| Serotonin 2b (5-HT2b) receptor           | HTR2B      | P41595    | CHEMBL1833        | 0.082222     | 0 / 1              |
| Alpha-2a adrenergic receptor             | ADRA2A     | P08913    | CHEMBL1867        | 0.082222     | 0 / 1              |
| Common name | Uniprot ID | ChEMBL ID | Target Class | Probability* | Known actives (3D/2D) |
|-------------|------------|-----------|--------------|--------------|-----------------------|
| Adrenergic receptor alpha-2 | ADRA2C | P18825 | CHEMBL1916 | 0.082222 | 0 / 1Â Â Â Â Â |
| Alpha-2b adrenergic receptor | ADRA2B | P18089 | CHEMBL1942 | 0.082222 | 0 / 1Â Â Â Â Â |
| Dopamine D1 receptor | DRD1 | P21728 | CHEMBL2056 | 0.082222 | 0 / 1Â Â Â Â Â |
| MAP kinase ERK2 | MAPK1 | P28482 | CHEMBL4040 | Kinase | 0 / 111 / 0Â Â Â Â Â |
| Sodium/glucose cotransporter 1 | SLC5A1 | P13866 | CHEMBL4979 | Electrochemical transporter | 0 / 138 / 0Â Â Â Â Â |
| Sodium/glucose cotransporter 2 | SLC5A2 | P31639 | CHEMBL3884 | Electrochemical transporter | 0 / 464 / 0Â Â Â Â Â |
| P2X purinoceptor 3 | P2RX3 | P56373 | CHEMBL2998 | Ligand-gated ion channel | 0 / 135 / 0Â Â Â Â Â |
| Dual specificity mitogen-activated protein kinase 1 | MAP2K1 | Q02750 | CHEMBL3587 | Kinase | 0 / 95 / 0Â Â Â Â Â |
| DNA topoisomerase I | TOP1 | P11387 | CHEMBL1781 | Isomerase | 0 / 21 / 0Â Â Â Â Â |
| GABA receptor alpha-5 subunit | GABRA5 | P31664 | CHEMBL5112 | Ligand-gated ion channel | 0 / 45 / 0Â Â Â Â Â |
| Dual specificity phosphatase Cdc25B | CDC25B | P30305 | CHEMBL4804 | Phosphatase | 0 / 5 / 0Â Â Â Â Â |
| Interleukin-1 receptor-associated kinase 4 | IRAK4 | Q9NWZ3 | CHEMBL3778 | Kinase | 0 / 63 / 0Â Â Â Â Â |
| Serine/threonine-protein kinase mTOR | MTOR | P42345 | CHEMBL2842 | Kinase | 0 / 182 / 0Â Â Â Â Â |
| Adenosine A1 receptor (by homology) | ADORA1 | P30542 | CHEMBL226 | Family A G protein-coupled receptor | 0 / 762 / 0Â Â Â Â Â |
| Adenosine A3 receptor | ADORA3 | P0DMS8 | CHEMBL256 | Family A G protein-coupled receptor | 0 / 401 / 0Â Â Â Â Â |
| Epidermal growth factor receptor erbB1 | EGFR | P00533 | CHEMBL203 | Kinase | 0 / 94 / 0Â Â Â Â Â |
| Homoorientin | Common name | Uniprot ID | ChEMBL ID | Target Class | Probability* | Known actives (3D/2D) |
|--------------|-------------|------------|-----------|--------------|--------------|----------------------|
| Adenosine kinase | ADK | P55263 | CHEMBL3589 | Enzyme | 0.106543 | 2 / 7 |
| Equilibrative nucleoside transporter 1 | SLC29A1 | Q99808 | CHEMBL1997 | Electrochemical transporter | 0.106543 | 0 / 0 |
| Homoorientin | Common name | Uniprot ID | ChEMBL ID | Target Class | Probability* | Known actives (3D/2D) |
| Beta-glucocerebrosidase | GBA | P04062 | CHEMBL2179 | Enzyme | 0.106543 | 2 / 7 |
| | PSEN2 | P49810 | | | | |
| | PSENEN | Q9NZ42 | | | | |
| | NCSTN | Q92542 | | | | |
| | APH1A | Q96B13 | | | | |
| | PSEN1 | P49768 | | | | |
| Gamma-secretase | APH1B | Q8WW43 | CHEMBL2094135 | Protease | 0.106543 | 0 / 14 |
| P-glycoprotein 1 | ABCB1 | P08183 | CHEMBL4302 | Primary active transporter | 0.106543 | 0 / 22 |
| Adenosine A1 receptor (by homology) | ADORA1 | P30542 | CHEMBL226 | Family A G protein-coupled receptor | 0.106543 | 60 / 0 |
| Vascular endothelial growth factor A | VEGFA | P15692 | CHEMBL1783 | Secreted protein | 0.106543 | 0 / 1 |
| Acidic fibroblast growth factor | FGF1 | P05230 | CHEMBL2120 | Secreted protein | 0.106543 | 0 / 1 |
| Basic fibroblast growth factor | FGF2 | P09038 | CHEMBL3107 | Secreted protein | 0.106543 | 0 / 1 |
| Heparanase | HPSE | Q9Y251 | CHEMBL3921 | Enzyme | 0.106543 | 0 / 1 |
| Caspase-3 | CASP3 | P42574 | CHEMBL2334 | Protease | 0.106543 | 41 / 0 |
| Caspase-6 | CASP6 | P55212 | CHEMBL3308 | Protease | 0.106543 | 7 / 0 |
| Caspase-7 | CASP7 | P55210 | CHEMBL3468 | Protease | 0.106543 | 7 / 0 |
| Caspase-8 | CASP8 | Q14790 | CHEMBL3776 | Protease | 0.106543 | 9 / 0 |
| Caspase-1 | CASP1 | P29466 | CHEMBL4801 | Protease | 0.106543 | 11 / 0 |
| Sodium/glucose cotransporter 1 | SLC5A1 | P13866 | CHEMBL4979 | Electrochemical transporter | 0.106543 | 24 / 0 |
| Epoxide hydratase | EPHX2 | P34913 | CHEMBL2409 | Protease | 0.106543 | 3 / 0 |
Narirutin is a flavonoid and has anti-inflammatory and anti-oxidative properties (Salehi et al. 2019). Scutellarin is a flavone glycoside and has antioxidant, antitumor, antiviral, and anti-inflammatory properties (Chan and, Carine S. S. Lim, Win Yee Lim, Zhi Juin Loong 2019). Scutellarin-rich extract, known as breviscapine, has been used as a medicine to improve blood circulation and cerebral blood supply. Complanatuside has anti-inflammation, lipid-lowering and hepatoprotective properties. Complanatuside pharmacokinetic analysis has been developed and validated (Yao et al. 2018). Eriocitrin flavanone has beneficial health effects and has antioxidant activity (Cesari et al. 2020); as many of these compounds, low water solubility, stability and shelf life are major issues of eriocitrin. Studies have focused on improving these aspects. OroxinB has been studied as a therapeutic agent for liver cancer. Based on Microfluidic Chip and DEN-induced rat model, OroxinB effectively exerts anti-liver cancer effect both in vitro and in vivo. The expression of miR-221 in OroxinB treated groups was significantly lower than that in the control group(Li et al. 2019). Homoorientin (Isoorientin), a flavone, has been demonstrated to have anti-cancer activities against various tumours (Quilez et al. 2018; Ye et al. 2016).

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