An In silico approach for the identification of GRB2 inhibitors for the treatment of Polycystic ovary syndrome (PCOS)

Anshika Agarwal[1], Anuraj Nayarisseri[1,2,*]

Corresponding author: anuraj@eminentbio.com; Tel: +91 9752295342

1. *In silico* Research Laboratory, Eminent Biosciences, Mahalakshmi Nagar, Indore – 452010,Madhya Pradesh, India.
2. Bioinformatics Research Laboratory, LeGene Biosciences Pvt Ltd., Mahalakshmi Nagar, Indore - 452010, Madhya Pradesh, India.

Background:

Polycystic Ovary Syndrome (PCOS) is extremely prevalent and diverse. It is the most commonly encountered heterogeneous endocrine disorder in premenopausal (reproductive age) women worldwide.[1] Studies shows that it affects 5-10% of this population.[2] It is a characteristic syndrome of ovarian dysfunction associated with hyperandrogenism, chronic anovulation, endometrial hyperplasia and significant morbidity. Many other crucial body systems are also affected causing hirsutism, infertility, alopecia, menstrual irregularities and obesity.[3] The aetiology of this syndrome is still debatable. Although it is found that PCOS is common among middle and high-income urban population rather than in the rural population.[5]The women with PCOS have a higher risk of developing type 2 diabetes mellitus and impaired glucose tolerance at an early stage.[4]Insulin resistance is the key feature of PCOS and it is characterised by hyperinsulinemia. Obese women are at a higher risk of developing insulin resistance than normal-weight women and have higher hyperandrogenism.[6]

The growth factor receptor-bound protein-2 (GRB2) is an adapter protein and is essential for cellular functions. It can either promote or block the cellular transformation and proliferation depending upon its activation and inhibition respectively. It plays a critical role in linking cell surface growth receptors (EGFR) and the Ras signalling pathway.[7]

It is very crucial to curb the overexpression of the protein by using a potent ligand to activate essential cellular functions. It is used to comprehend the strength of association and the binding affinity between the appropriate ligands and the target binding site. This helps to develop more efficient drug candidates which would essentially help in the curing of the syndrome. The aim of the present investigation is to identify a potential GRB2 inhibitor

towards the clinical treatment of Polycystic ovary syndrome (PCOS) using various molecular docking[8-15] and virtual screening approaches[16-28].

Keywords: Polycystic ovary syndrome (PCOS), GRB2, GRB2 inhibitors, Molecular Docking, Virtual Screening, ADMET.

REFERENCES:

1. Enrico Carmina, Rogerio A. Lobo, Polycystic Ovary Syndrome (PCOS): Arguably the Most Common Endocrinopathy Is Associated with Significant Morbidity in Women, *The Journal of Clinical Endocrinology & Metabolism*, Volume 84, Issue 6, 1 June 1999, Pages 1897–1899, https://doi.org/10.1210/jcem.84.6.5803
2. Bharathi, R. Vidya, et al. "An epidemiological survey: Effect of predisposing factors for PCOS in Indian urban and rural population." Middle East Fertility Society Journal 22.4 (2017): 313-316.
3. Norman, Robert J., et al. "Polycystic ovary syndrome." *The Lancet* 370.9588 (2007): 685-697.
4. Dunaif, A., Wu, X., Lee, A., &Diamanti-Kandarakis, E. (2001). Defects in insulin receptor signalling in vivo in the polycystic ovary syndrome (PCOS). *American Journal of Physiology-Endocrinology And Metabolism*, *281*(2), E392-E399.
5. Bharathi, R. Vidya, et al. "An epidemiological survey: Effect of predisposing factors for PCOS in Indian urban and rural population." Middle East Fertility Society Journal 22.4 (2017): 313-316.
6. A. Gambineri, C. Pelusi, V. Vicennati, U. Pagotto, and R. Pasquali, “Obesity and the polycystic ovary syndrome,” International Journal of Obesity, vol. 26, no. 7, pp. 883–896, 2002.
7. Tari, Ana M., and Gabriel Lopez-Berestein. "GRB2: a pivotal protein in signal transduction." Seminars in oncology. Vol. 28. WB Saunders, 2001.
8. Limaye, A., Sweta, J., Madhavi, M., Mudgal, U., Mukherjee, S., Sharma, S., Hussain, T., Nayarisseri, A. and Singh, S.K. (2019). In Silico Insights on GD2: A Potential Target for Pediatric Neuroblastoma. Current topics in medicinal chemistry, 19(30), 2766-2781.
9. Nayarisseri, A. (2019). Prospects of Utilizing Computational Techniques for the Treatment of Human Diseases. Current topics in medicinal chemistry, 19(13), 1071-1074.

10. Nayarisseri, A. and Hood, E.A., 2018. Advancement in microbial cheminformatics. Current topics in medicinal chemistry, 18(29), pp.2459-2461.
11. Monteiro, A.F.M., Viana, J.D.O., Nayarisseri, A., Zondegoumba, E.N., Mendonça Junior, F.J.B., Scotti, M.T. and Scotti, L., 2018. Computational studies applied to flavonoids against alzheimer's and parkinson's diseases. Oxidative medicine and cellular longevity, 2018.
12. Sahila, M. M., Babitha, P. P., Bandaru, S., Nayarisseri, A., & Doss, V. A. (2015). Molecular docking based screening of GABA (A) receptor inhibitors from plant derivatives. Bioinformation, 11(6), 280.
13. Bandaru, S., Tarigopula, P., Akka, J., Marri, V.K., Kattamuri, R.K., Nayarisseri, A., Mangalarapu, M., Vinukonda, S., Mundluru, H.P. and Sagurthi, S.R. (2016). Association of Beta 2 adrenergic receptor (Thr164Ile) polymorphism with Salbutamol refractoriness in severe asthmatics from Indian population. Gene, 592(1), 15-22.
14. Khandekar, N., Singh, S., Shukla, R., Tirumalaraju, S., Bandaru, S., Banerjee, T., &Nayarisseri, A. (2016). Structural basis for the in vitro known acyl-depsipeptide 2 (ADEP2) inhibition to Clp 2 protease from Mycobacterium tuberculosis. Bioinformation, 12(3), 92.
15. Bandaru, S., Alvala, M., Nayarisseri, A., Sharda, S., Goud, H., Mundluru, H. P., & Singh, S. K. (2017). Molecular dynamic simulations reveal suboptimal binding of salbutamol in T164I variant of β2 adrenergic receptor. PloS one, 12(10), e0186666.
16. Sharda, S., Sarmandal, P., Cherukommu, S., Dindhoria, K., Yadav, M., Bandaru, S., &Nayarisseri, A. (2017). A Virtual Screening Approach for the Identification of High Affinity Small Molecules Targeting BCR-ABL1 Inhibitors for the Treatment of Chronic Myeloid Leukemia. Current topics in medicinal chemistry, 17(26), 2989-2996.
17. Divya Jain, T. U., Shreshtha Sharma, AishwaryaGandhe, Palugulla Bhaskar Reddy, Anuraj Nayarisseri, Sanjeev Kumar Singh (2019). "Design of novel JAK3 Inhibitors towards Rheumatoid Arthritis using molecular docking analysis." Bioinformation 15(2): 68-78.
18. Mendonça-Junior, F. J., Scotti, M. T., Nayarisseri, A., Zondegoumba, E. N., & Scotti, L. (2019). Natural Bioactive Products with Antioxidant Properties Useful in Neurodegenerative Diseases. Oxid Med Cell Longev, 2019, 1-2.
19. Nayarisseri, A. and E. Hood (2018). "ADVANCEMENT IN MICROBIAL CHEMINFORMATICS." Current topics in medicinal chemistry. 18(29):2459-2461.

20. Padmini Gokhale, A. P. S. C., Anushka Arora, Natasha Khandekar, Anuraj Nayarisseri, Sanjeev Kumar Singh (2019). "FLT3 inhibitor design using molecular docking based virtual screening for acute myeloid leukemia." Bioinformation 15(2): 104-115.
21. Palak Shukla, R. K., Diksha Sharma, AnindyaDhar, Anuraj Nayarisseri, Sanjeev Kumar Singh (2019). "Virtual Screening of IL-6 Inhibitors for Idiopathic Arthritis." Bioinformation 15(2): 121-130.
22. TrishangUdhwani, S. M., Khushboo Sharma, JajoriyaSweta, Natasha Khandekar, Anuraj Nayarisseri, Sanjeev Kumar Singh (2019). "Design of PD-L1 inhibitors for lung cancer." Bioinformation 15(2): 139-150.
23. Rao, D. M., Nayarisseri, A., Yadav, M., & Patel, D. (2010). Comparative modeling of methylentetrahydrofolate reductase (MTHFR) enzyme and its mutational assessment: in silico approach. International Journal of Bioinformatics Research, 2(1), 5-9.
24. Kelotra, S., Jain, M., Kelotra, A., Jain, I., Bandaru, S., Nayarisseri, A., &Bidwai, A. (2014). An in silico appraisal to identify high affinity anti-apoptotic synthetic tetrapeptide inhibitors targeting the mammalian caspase 3 enzyme. Asian Pac J Cancer Prev, 15(23), 10137-10142.
25. Sweta J, Khandelwal R, Srinitha S, Pancholi R, Adhikary R, Ali MA, Nayarisseri A, Vuree S, Singh SK. (2019). Identification of High-Affinity Small Molecule Targeting IDH2 for the Clinical Treatment of Acute Myeloid Leukemia.Asian Pac J Cancer Prev.20(8),2287-2297.
26. Gutlapalli, V. R., Sykam, A., Nayarisseri, A., Suneetha, S., &Suneetha, L. M. (2015). Insights from the predicted epitope similarity between Mycobacterium tuberculosis virulent factors and its human homologs. Bioinformation, 11(12), 517.
27. Nayarisseri, A., Yadav, M., &Wishard, R. (2013). Computational evaluation of new homologous down regulators of Translationally Controlled Tumor Protein (TCTP) targeted for tumor reversion. Interdisciplinary Sciences: Computational Life Sciences, 5(4), 274-279.
28. Praseetha, S., Bandaru, S., Nayarisseri, A., &Sureshkumar, S. (2016). Pharmacological Analysis of Vorinostat Analogues as Potential Anti-tumor Agents Targeting Human Histone Deacetylases: an Epigenetic Treatment Stratagem for Cancers. Asian Pacific Journal of Cancer Prevention, 17(3), 1571-1576.