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A Comprehensive Review on in Silico Computational Studies of Siddha Formulations Against Sars – Cov- 2

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Abstract

The global current scenario shows that COVID-19 has spread worldwide and drugs prescribed to treat the disease are under study. The imperative requirement of drugs to treat COVID-19 has made significant changes in the pharmacological industry. Discovering drugs for such a pandemic has been a crucial target, with standardisation, preclinical and clinical studies being conducted in all possible age groups. Siddha medicines have found their way in the treatment of COVID-19 largely and increasingly been accepted worldwide. Among such constant trials, implementation of the molecular docking process has helped to reveal the importance of different Siddha medicines in the first place as therapeutics to COVID-19. The Government bodies have also recommended these antiviral compounds to treat symptoms such as cold, fever, breathing difficulty and sore throat. This study aims to focus on to gather awareness on the impact of various Siddha medicines and their insights into molecular level to fight against Coronaviruses. As a result of this review, it was found that the phytochemical compounds present in various siddha medicines such as Kabasura Kudineer, Adathodai Kudineer, Maramanjal Kudineer and so on, have been docked with the possible target proteins of SARS-CoV-2 virus to disclose that they have potential action on the virus and declare to act as the candidate drugs in COVID-19 treatment.

Keywords: COVID-19, Siddha medicine, Kabasura Kudineer, SARS-CoV2, Molecular Docking, Kabasura Kudineer, Adathodai Kudineer

Introduction

COVID-19 has been announced as the global pandemic by the World Health Organisation (WHO) in 2019. It has been estimated that during this pandemic situation, about 219 countries have been affected with about 211,373,303 positive cases (WHO, 2021) and 4,424, 341 deaths reported. On a positive note nearly 7,032,000 people have recovered from this disease. Researchers report that COVID-19 is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) that leads to acute respiratory illness among the affected people. Nearly 7 different types of Human CoronaVirus (HCoV) have been identified and it has been categorised to cause human infections. They are classified into two different forms and these are alpha and beta CoVs. β -CoV (OC43, HKU1, SARS, MERS and COVID-19 HCoVs) and α-CoV (229E and NL63). MERS and SARS CoV are found to be more virulent **[1] [2].**

The current paper will focus on the importance of the molecular docking system carried out on Siddha formulations to act against SARS CoV-2 virus thereby recognised as efficient treatment for COVID-19. Moreover, this study will focus on the impact of technological innovation to implement In Silico computational studies for Siddha formulations. The formulation methods will be discussed to understand the accuracy of the in silico docking studies for COVID-19 treatment.

Aim and objectives

The primary objective of the review is to analyse the Molecular Docking Study of Siddha formulations and the thereby disclosing importance of the Siddha formulations against SARS-CoV2. The study also aims,

- To identify the impact of the molecular docking study for Siddha formulation.
- To determine the effectiveness of the Siddha for treating Covid 19
- To recognize the importance of the In Silico computational studies in Siddha formulations

Methodology:

The databases such as Medline/PubMed Central/PubMed, Science Direct, Scopus, Web of science, Google Scholar, Directory of open access journals (DOAJ), EMBASE, have been referred to make out distinct articles in relevant to the in-silico studies that are performed in Siddha formulations against the proteins of SARS CoV-2 virus. The review reports were collected and presented in this study

Implications of Molecular docking study:

Molecular docking is one of the key tools to enhance knowledge of structural and molecular biology and computer aided drug design. The DHA medicine is used for the eradication of respiratory infection. It has been detected that this medicine consists of antiviral compounds. Since the Corona virus is spreading according to the wave pattern, the traditional drug discovery method is quite ineffective for this respiratory infection. The implementation of the molecular docking process has capabilities for large scale screening to launch effective medicines to get proper treatment from the disease **[3].** Molecular docking study basically relies on computational algorithms to predict the drug potency. This drug efficacy would be determined based on the binding of the ligand with the target protein **[4].**

Recognition of the Siddha medicine formulation method helps to determine the authenticity of the medicines. Furthermore, the Molecular Docking Studies is able to provide huge information on the molecular factors of the medicines to enhance the effectiveness of these medicines. The In silico docking process is used to select the target protein and reveals the potential role of phytochemicals present in the formulations. Selection of protein is the crucial factor in docking studies wherein the ligand preparation is also beneficial to predict the active Site for launching effective medicines against Coronaviruses**.**

Identification of the molecular structure and bonding helps to determine the effective components of the medicine. Molecular Docking Study (MDS) is significantly important to find the compounds present in the medicines and their effects on the COVID-19 treatment. This MDS not only facilitates numerous people at a time but also helps to continue the further wet-lab experiments with the help of computer software. Moreover, this process is significantly cost-effective than the traditional method **[5].** In Silico prediction is important to enhance the research on pharmacokinetics. It is able to provide safety guidelines to the patients for the eradication of the harmful effects of the medicines.

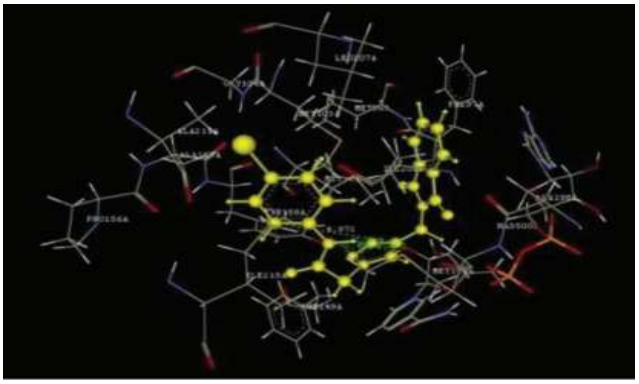

Figure 1: Molecular docking

(Source: Phatak *et al.* 2020)

The development of the structure-based drug design (SBDD) helps to follow a complementary and specific method to manufacture appropriate drugs for treating COVID- 19. Appropriate pharmacological activities are needed to identify the activity level and the relative position of the drugs. The In Silico design is divided into four different categories; these are ligand-based, combinatorial, receptor - based and the denovo based. This provides a detailed information on the MDS methods or structure to determine the

effectiveness of the medicines**.** Gathering knowledge on the MDS helps in the identification of pharmacophore and modification of the pharmacophore to fit at the receptor, for determination of the drug's potentiality. According to these articles, the MDS process aims to achieve relative orientation and optimised conformation between the effective protein and ligands. There are two primary factors for the regulation of the MDS process, the intramolecular forces, such as bond length, dihedral angle and bond angle and the intermolecular forces, dipolar, hydrophobic, electrostatic. H bonding and Vander waals forces **[6].**

The MDS is essential to enhance the competence of molecular biology to identify appropriate medicines for the disease. The entire medical research centre is using this ultra-modern technological innovation like MDS against the Coronavirus. Using this strategy has helped to formulate Siddha medicines against Coronavirus. According to these articles, the use of the Cresset Flare software is significantly important to enhance the proactivity of the MDS in the pharmaceutical industry **[7].**

Potential targets of SARS CoV-2:

The determination of SARS CoV2 virus proteins can serve as a potential target for the development of drugs and vaccines. It consists of a number of Non structural proteins (Nsp1, Nsp3, Nsp5, Mpro, Nsp7, Nsp8, Nsp9, Nsp10, Nsp12, Nsp13, Nsp14, Nsp15, Nsp16), RNA Dependent RNA Polymerase (RdRP), Spike protein (S), Nucleocapsid protein (N), Membrane (M) & Envelope (E) protein and certain ORFs **[8].** The structure of 3CLpro/Mpro (PDB ID: 6LU7) of SARS CoV-2 protein was retrieved from Protein Data Bank. After the selection of protein, the next stage is ligand preparation and it is significantly important for the development of the 2D and 3D structures of the ligands to visualise the result of the hydrogen interactions with the protein bonds. Different bioactive constituents are used for the ligand preparations, such as β-Sesquiphellandrene, Geranial, Piperlonguminine, 3-(2, 4- dimethoxy phenyl)-6, Andrograpanin, β-Bisabolene and many others. It has been detected that about 145 effective Phyto compounds have been selected from the Kabasura Kudineer. The ACD chem sketch is used to generate the 145 two dimensional ligands. According to the research paper, the OPEN BABEL software is used to convert the ligands into pdb format **[9].** After the ligand preparation, the next stage is the prediction of the active site it is one of the crucial stages in the molecular docking process. This is further subjected to Protein-ligand docking**,** to develop a virtual screening for managing the protein binding activities with efficiency. Visualisation and making compound structures of these proteins are required to determine the binding energies of the compounds to the target.

Siddha Formulations in treating COVID-19

Siddha is an ancient system Indian traditional medicine (ITM) of South Indian Origin, which is increasingly being accepted and advocated in the current Coronavirus pandemic situation. The Government of India, Ministry of AYUSH has introduced the Siddha practitioner's guidelines for treatment against the COVID-19. Siddha is intended to not only eradicate the infection of SARS CoV-2, but also to cure this disease with precision**.** A number of Siddha formulations are now in clinical practise for treating COVID symptoms such as Kabasura Kudineer Chooranam, Amukkara Chooranam, Brammananda Bhairavam maathirai, Adathodai manappagu, etc. It has been reported that these medicines are able to treat many patients in India, notably in South India. Kabasura Kudineer decoction given to COVID positive patients has made it very beneficial for thousands of people and is also given as a precautionary measure to avoid getting infected by the SARS-CoV-2 virus.

Kabasura kudineer and naga parpam with adjuvants like *Emblica officinalis* juice are also prescribed for fever and respiratory ailments. Besides these medicines, increased concentration of Zinc is also identified to impair the replication of the virus inside the host cells **[10].**

Formulations like Kabasura Kudineer is reported to have antipyretic, antiviral, antioxidant, hepatoprotective and immunomodulatory effects while Nilavembu Kudineer also has antipyretic, antiviral, antioxidant, immunostimulant and immunomodulatory effects. Furthermore, Thonthasura Kudineer has antiviral, anti-asthmatic, hepatoprotective and immunomodulatory effects. Visha sura kudineer is reported to have antiviral, anti-asthmatic, immunostimulant, antioxidant properties and Adathodai manapagu has anti-pyretic, anti-inflammatory, antioxidant, anti inflammatory and hepatoprotective activity **[11].** These reports illustrate the efficacy of siddha formulations in treating diseases **[12].**

Kabasura Kudineer:

One of the classical preparations of Siddha, Kabasura kudineer is prescribed widely for its antiviral activity and for respiratory ailments. The physicochemical and phytochemical studies done on Kabasura Kudineer proves its efficacy as an antiviral, anti-inflammatory and antipyretic effects **[13].**

One of the important siddha formulations given as a therapeutic for COVID-19 is **Kabasura Kudineer.** It is in currently in clinical practise to treat conditions like GIT and bacterial infections. It was one of the effective medicines that is most predominantly used to treat COVID-19 patients. This polyherbal formulation is made up of nearly fifteen herbal ingredients. Molecular Docking Studies on Kabasura Kudineer has been conducted to determine the efficiency of the medicine. The phytochemicals were obtained using SMILES string method from PubChem. Molecular Docking was done using Chimera v1.14 and AutoDock Vina v1.12 platform. In the study conducted, it was reported that the phytochemicals Terflavin B from Kadukkaithol had higher binding energy to RdRp and spike protein while Ellagic acid bound effectively with protease of SARS CoV-2. Among the 15 herbs, 6 were found to have potential action against RdRP. Hence, Kabasura Kudineer chooranam is found to have high antiviral activity against SARS CoV-2 **[9].**

Another study reported on the comparative analysis of two siddha formulations Kabasura Kudineer and Thonthasura Kudineer claims strong evidence on Kabasura Kudineer as a potential drug of choice. In silico docking studies was done for the phytocomponents of both the formulations against coronavirus spike glycoprotein -PDB ID: 3JCL on iGEMDOCK platform. The study report showed that the phytocompounds of Kabasura Kudineer bound the viral proteins effectively than Thonthasura Kudineer **[14].**

Siddha Medicines are classically used for hundreds of years now and many are currently proved to have antibacterial as well as antiviral properties. In one of the study, the siddha formulation Kabasura Kudineer and a novel preparation JACOM were subjected to docking studies on the Cresset Flare software platform. Furthermore, Pharmacokinetics and safety profile testings were also done for the above preparations. Results showed that out of 37 phytochemical compounds screened, 9 of them showed high binding affinity towards the spike protein of the virus. This illustrates that these formulations may have potential antiviral properties against SARS CoV-2 virus **[15].**

Ammaiyar Koonthal Kudineer:

Apart from the Kabasura Kudineer, there are many Siddha medicines, which help to eradicate the risk factors of Corona as the herbal sources are important to develop antiviral properties in the human body to eradicate the risk factors of Coronavirus. Ammaiyar Koondhal Kudineer (Akk) is a polyherbal Siddha formulation used to treat toxic fever with severe symptoms, skin diseases and constipation. Molecular docking studies were conducted with the phytochemicals of Ammaiyar Koonthal Kudineer and the proteins of SARS CoV-2. The phytochemicals were obtained from PubChem. Docking procedures were performed using AutoDock Vina v1.12 platform. The results shows that among all the docked phytochemicals, chebulagic acid bound effectively with SARS CoV-2 spike protein and spike protein bound with ACE2

receptor complex. This shows that chebulagic acid is the highly potent compound present in Ammaiyar Koonthal Kudineer that acts against the virus **[16].**

Adathodai Kudineer:

Another most predominant siddha formulation Adathodai Kudineer is one of the effective herbal medicines against the Coronavirus. Adathodai Kudineer mainly consists of four herbs used to treat clinical conditions like asthma and intense cough. This formulation was also predominantly used in the treatment of COVID-19 and hence was taken for docking studies against two main proteins- Spike protein and ACE2 receptor spike protein complex. The phytochemicals of Adathodai Kudineer were retrieved from PubChem and the docking studies were performed using AutoDock Vina v1.12 platform. Results evidenced that among the eighteen phytochemicals that were docked, Alpha-copaene was found to have higher binding energy towards SARS CoV-2 spike protein and ACE2 receptor complex. This shows that Adathodai Kudineer has high affinity towards the viral proteins **[17].**

Maramanjal Kudineer Chooranam:

Maramanjal Kudineer Choornam, another significant Siddha formulation consists of fifteen herbal ingredients. It is prescribed for clinical conditions including diabetes, skin diseases and jaundice. Maramanjal Kudineer chooranam (MKC) was taken to molecular docking studies to evaluate its efficacy as a potential drug of choice for the treatment of COVID-19 disease. The 74 phytochemicals retrieved from its ingredients were subjected to molecular docking using AutoDock 4 platform. Results showed that many of the active constituents had excellent binding affinity with the main protease and RNA dependent RNA Polymerase (RdRP). Hence MKC was found to be effective against the main Protease and RdRP of SARS CoV-2 virus **[18].**

Phytochemicals of Siddha Formulations:

Siddha polyherbal formulations are in use for trating a variety of bacterial and viral infections. Among them Kabasura Kudineer, Thonthasura Kudineer and Vishasura kudineer are of most prevalent use in clinical practise for the treatment of viral fever and respiratory illnesses. The phytochemicals present in these three siddha formulations were subjected to molecular docking studies to the targets M^{Pro} (PDB ID 5R82, 6Y2F, and 6LU7), Nsp15 endoribonuclease (6W01), RNA-dependent RNA polymerase (6M71), and spike protein (6VW1) of SARS-CoV-2 virus. It was found that out of the 36 phytochemical compounds that were docked, 9 of them had high binding affinity and witnessed to be served as potential antiviral agents **[19].**

Kadukkai Ooral Kudineer, made of soaked water of *Termnalia chebula* is also reported to be one of the important remedy for the treatment of COVID-19 infection. Terminalia chebula possess immunomodulatory, anti-oxidant, anti-inflammatory and anti-viral property and hence may boost host immunity during the course of the disease **[20].**

The phytochemical compounds of ten Indian herbal medicinal plants were screened for Molecular docking studies to the target MPro, Spike protein and ACE2 receptor. It is reported that phytochemicals such as Cucurbitacin E, Orientin, Bis-andrographolide, Cucurbitacin B, Isocucurbitacin B, Vitexin, Berberine, Bryonolic acid, Piperine and Magnoflorine were found to bind effectively with the SARS CoV-2 proteins and therefore may have antiviral potential **[21].**

Conclusion

The current review paper has focused on the Indian Traditional system, Siddha medicines against the SARS CoV-2 virus. Increasing drug demands has adopted technological and modern drug discovery processes for treating COVID patients. These discoveries not only turned out to decrease the mortality rate but also

played a major role in boosting the immune system. Identification of the molecular or chemical structure helped to find out the effectiveness of these products for the enhancement of pharmacological knowledge and growth. The aim of the study was to establish the critical role of siddha formulations in COVID-19 treatment through Molecular docking studies. The review has evidenced many siddha formulations like Kabasura Kudineer chooranam, Nilavembu Kudineer chooranam, Adathodai Kudineer chooranam, Maramanjal kudineer chooranam and so on as potential agents in COVID-19 treatment. Besides these formulations, single herb medicines like Kadukkaithol ooral kudineer and other such concoctions are also identified as effective therapeutics for COVID both as antiviral agents and also immunomodulators. Furthermore, from the present review it has been perceived that the molecular docking process is more reliable, cheaper and faster than any kind of conventional processes of identification of a potential candidate drug. On conclusion, this study throws light on the efficacy of siddha formulations at molecular biology level and also paves way for further preclinical and clinical trial of the suggested formulations.

References

1. WHO, 2021, Novel coronavirus 2019. https://www.who.int/emergencies/diseases/novel-coronavirus-2019
2. P. Prakash, R. Meena, L. Stanley Abraham, Swetha Sunkar, K. Govindaraju, Durgasruthi Pully, Antony V. Samrot. (2021). Evidence-based traditional Siddha formulations for prophylaxis and management of respiratory symptoms in COVID-19 pandemic- A review. Biocatalysis and Agricultural Biotechnology. 35: 102056. https://doi.org/10.1016/j.bcab.2021.102056
3. Meng X. Y., Zhang, H. X., Mezei, M., and Cui, M. (2011) Molecular docking: a powerful approach for structure-based drug discovery. Curr Comput Aided Drug Des. 7(2), 146-157. doi:10.2174/157340911795677602
4. Phatak, P.S., Bakale, R.D., Dhumal, S.T., Dahiwade, L.K., Choudhari, P.B., Siva Krishna, V., Sriram, D. and Haval, K.P., (2019). Synthesis, antitubercular evaluation and molecular docking studies of phthalimide bearing 1, 2, 3-triazoles. Synthetic communications, 49 (16), pp. 2017-2028.
5. Vamshi Ram V, Premavathy D and Preetha S. (2020). Assessing of knowledge of Siddha medicine having antiviral property. European Journal of Molecular & Clinical Medicine, 7(01), p.2020.
6. Laila H, Abdel Rahman, Ahmed M. Abu Dief, Mohamed R. Shehata, Faten M. Atlam, Azza A. Hassan and Abdel Mawgoud. (2019). Some new Ag (I), VO (II) and Pd (II) chelates incorporating tridentate imine ligand: Design, synthesis, structure elucidation, density functional theory calculations for DNA interaction, antimicrobial and anticancer activities and molecular docking studies. Applied Organometallic Chemistry, 33(4), p. e4699.
7. https://doi.org/10.1002/aoc.4699
8. Ponnam, H.B. and Akondi, B.R. (2020). AYUSH Systems of Medicine, a Viable Solution for COVID-19 amidst the Uncertainty of Vaccination and Herd Immunity-An Indian Perspective. Asian Journal of Pharmaceutical Research and Health Care, 12(2), pp.52-54.
9. Rimanshee Arya, Shweta Kumari, Bharati Pandey, Hiral Mistry, Subhash C. Bihani, Amit Das, Vishal Prashar, Gagan D. Gupta, Lata Panicker, and Mukesh Kumar. (2021). Structural insights into SARS-CoV-2 proteins. J Mol Biol. Jan 22; 433(2): 166725. doi: 10.1016/j.jmb.2020.11.024
10. Vincent S., Arokiyaraj S., Saravanan M. and Dhanraj M. (2020). Molecular docking studies on the anti-viral effects of compounds from Kabasura Kudineer on SARS-CoV-2 3CLpro. Frontiers in molecular biosciences, 7, p.434.
11. Gnanavel, Rameshkumar, R. and Balasubramanian, P.L. (2020). Combating Coronavirus Disease 2019 (COVID-19) Through Siddha System of Medicine. Journal of Siddha, 4(1), pp.1-8.
12. Sabarianandh JV, Bernaitis L, Manimekalai K. (2020). COVID-19 in Siddha Medicine: A Review. J Basic Clin Appl Health Sci; 3(2):83–86.

13. Thillaivanan.S, Mubarak H, Susikannamma. S, Parthiban. P. (2021). A Review on Siddha Sastric Medicines Effective In Covid-19 Management at TPEC Covid Care Centre, Vellore. International Journal of Ayurveda and Pharma Research, p.56-61.
14. Ananya, B. and Arivarasu, L. (2020). Role of Kabasura Kudineer against Covid-19- A Review. Journal of Contemporary Issues in Business and Government, 26(2), pp.1212-1218
15. Pitchiah Kumar, M., Sundaram, K.M. and Ramasamy, M.S. (2019). Coronavirus spike (S) glycoprotein (2019-ncov) targeted siddha medicines Kabasura Kudineer and Thonthasura Kudineer–in silico evidence for corona viral drug. AJPRHC, 11, pp.1-9.
16. Gangarapu Kiran , L Karthik , M S Shree Devi , P Sathiyarajeswaran , K Kanakavalli , K M Kumar , D Ramesh Kumar . (2020). In Silico computational screening of Kabasura Kudineer - Official Siddha Formulation and JACOM against SARS-CoV-2 spike protein. J Ayurveda Integr Med. May 25; S0975-9476(20)30024-3. doi: 10.1016/j.jaim.2020.05.009
17. K. Rajamaheswari, Anand T, Mursaleen B, Vijai M, Jamyang P, K. Arunachalam, K. Venkateswaran, N. Kabilan, R.Meenakumari. (2020). In silico analysis of active compoundsfrom Siddha herbal infusion of Ammaiyar Koondhal Kudineer (Akk) against SARS CoV-2 Spike protein and its ACE2 receptor complex. https://ssrn.com/abstract=3578294
18. Gnanaraj Johnson, Christian and T, Anand and Krishnasamy, Rajamaheswari and Sekar, Priyanka and S, Elansekaran and Murugan, Ramamurthy and Ponnappan, Shanmugapriya and Ramasamy, Meenakumari. (2020). Phytochemical Screening of Adathodai Kudineer a Siddha Concoction and Evaluation of Binding Affinity of Its Constituents with SARS-CoV-2 Spike Protein and ACE2 Receptor Spike Protein Complex Through Molecular Docking In-Silico Approach. SSRN: https://ssrn.com/abstract=3607757
19. Suresh, Jerad and B, Kumudhaveni and S, Soundarya and G, Priyadharshini and Kaveripakkam Mohammed Ali, Noorulla. (2020). Screening of Siddha Herbal Formulation Maramanjal Kudineer Churnam Against COVID-19 Through Targeting of Main Protease and RNA-Dependent RNA Polymerase of SARS-CoV-2 by Molecular Docking Studies (July 23, 2020). SSRN: https://ssrn.com/abstract=3659092
20. Selvaraj, L.K., Thayumanavan, G., Jeyabalan, S. and Jabaris, S.L. (2021). Molecular Docking Studies of Phytoconstituents Identified in Traditional Siddha Polyherbal Formulations against Possible Targets of SARS-CoV-2. Journal of Molecular Docking, 1(1), pp.15-24.
21. Indhu, P.M., Sivakkumar, S., Mariappan, A. and Visweswaran, S. (2020). Kadukkai ooral Kudineer (Chebulic Soaked Water): Prophylactic Siddha Herbal Drink for Covid-19. Journal of Siddha, 4(1), pp.37-47.
22. Alagu Lakshmi, S., Shafreen, R.M.B., Priya, A. and Shunmugiah, K.P. (2020). Ethnomedicines of Indian origin for combating COVID-19 infection by hampering the viral replication: using structure-based drug discovery approach. Journal of Biomolecular Structure and Dynamics, pp.1-16.