

“Neem” (Azadirachta Indica) leaves as dietary supplement in treatment of COVID-19/SARS-CoV-2 : A Case Report

Dr Pallavi Moreshwar Kanitkar BAMS MS (Shalya), SAI Ayurvedha College, Vairag (MH), India

Shanmuga Subramanian B.E, Govt College of Engineering Tirunelveli, India.

Dr Neeta Deshpande MD (Dravyaguna)

Dr K.Shirish (MD)

Email: ramanean@gmail.com

Abstract:

These are some of the first known cases of SARS-CoV-2 (COVID-19) patients who recovered quickly and become asymptomatic after taking “Neem” leaves mixed with water as dietary supplement orally along with other standard prescribed line of treatment. The age group of patients in this study varies from 5 to 70 years with 2 children being aged 5 and 13 years , 3 adults were in the 36-40 age group and 1 adult was in the 60-70 age group. All the 6 of them had tested positive and the patients had typical COVID-19 symptoms like cough, bodyache, fever with 4 of them being symptomatic and the other 2 being asymptomatic. After taking Neem leaves mixed with water orally as dietary supplement in equal doses over 2 days, all of them had become asymptomatic and recovered fully clinically. There were 3 other people who took “Neem” leaves as prophylactic medication and tested “negative” , these people were in close contacts of the 69 yr. old patient. The treatment given above correlates with principles of “Jwara Chikitsa” in Ayurveda. Also nearly 25+ compounds in Neem leaves has shown high inhibition against COVID-19 Main Protease in the Molecular Docking study which shows compounds in Neem leaves has high inhibition against the virus. In addition to that Neem has been extensively used in Indian traditional medicine systems like Ayurvedha and Siddha for many centuries. Different research studies proves that Neem (Azadirachta Indica) is known to possess anti-viral properties and has been found to be effective against different viruses, as well as it is an well-known anti-inflammatory agent and also acts as an immunomodulator. Though this is a small case study done with 9 people, this would implore scientists and Governments around the world to look into Neem as an option for inhibiting COVID-19.

1.Introduction:

In December 2019, health officials at Wuhan, China reported a cluster of pneumonia cases within the city. Shortly after that they determined that the pneumonia was caused by virus which is of Zoonotic origin and it's caused by novel coronavirus. The virus is referred to SARS-CoV-2 and the disease caused by it is known as COVID-19. Initially there was an assumption that the virus transmission is happening only between animals to humans because the initial cases were related to Huanan Sea Food market but it was soon found out that the virus transmission also happens between humans. Soon it spread from China to other parts of the world .Each and every country was affected by COVID-19 . People around the world were affected directly and indirectly by it as the lockdowns imposed to prevent the spread of COVID-19 made the economies come to a standstill which lead to loss of jobs for millions of people leading to a worldwide recession. But till now no cure or drug has been found to prevent the spread of the virus and even some of the prominent drugs candidates also failed in clinical trials due to lot of reasons.

Neem in Ayurvedha/Siddha:

Neem also known as Azadirachta Indica (Nimtree or Indian lilac) is a tree in the mahogany family Meliaceae. It's one of the two species in the genus Azadirachta and is native to the Indian Sub-continent. It's mostly found in tropic and semi tropic regions around the world. Neem leaves, seeds, flowers are well known for its medicinal properties in India for centuries and there has been evidence of Neem being used for healing even 4500 years ago (1) in Ayurvedha and Siddha medicinal systems. In Sanskrit, Neem is called as Universal healer (**Sarva Roga Nivarini**) which means one that cures all ailments and ills. In Africa it's called as "40 cures". Neem leaves, fruits, flowers, oil from seeds has been used extensively in South East Asia to cure various diseases. And Neem is also known as Nimba which means 'bestower of good health'. The Neem leaf extracts have a powerful antiseptic, antifungal, antiviral and anti-bacterial effect.

unlike synthetic chemicals that often produce side effects such as allergic reactions, rashes etc.

2.Neem in Research papers:

Neem is not new to researchers around the world as it has been subject of around 3000 research papers all over the world and has been found to be effective against host of viruses, bacteria and also has been well known for its anti-inflammatory, anti-pyretic, anti-diabetic and other pharmacological properties. Let us see in more detail about the scientific research papers published on Neem and its uses.

2.1 Neem as an Anti-Viral

Neem leaves are well known for its anti-viral properties and has been used against viruses in Indian traditional medicinal systems like Ayurvedha, Siddha etc., Different research papers on Neem's effectiveness also proves the same. As of today, various research studies have proved Neem leaves to be effective against these viruses

- HIV (2) (3)
- HSV - Herpes Simplex Virus (4)
- Dengue (5) (6)
- Fowl pox viruses like Chickenpox, Smallpox (7)
- Cocksackie viruses which cause Hand, Foot & Mouth Disease (HFMD) (8)
- Hepatitis (9) (10)

Research has shown that Crude extracts of Neem leaves absorbed the viruses and effectively preventing them from entering the uninfected cells, thereby Neem leaves can be used a preventive medicine in inhibiting the virus from spreading to other uninfected cells. (11)

2.2 Neem as Anti-Inflammatory & Immunomodulator

Neem leaves are also known to possess anti-inflammatory and anti-proliferative properties and

various research papers prove that (12). In addition to that a comparative study of Neem and Dexamethasone indicated that Neem leaves does possess anti-inflammatory properties but not on the same scale as Dexamethasone (13) and also Neem leaves are known to act as Immunomodulators (14) (15) (16)

2.3 Anti-Diabetic properties of Neem

Research papers have also proven that Neem leaves & seeds also have anti-Diabetic properties by effectively lowering blood glucose level with minimal or no side-effects. They are known to possess hypolipidemic, hypoglycemic , immunostimulant and hepatoprotective properties (17) (18)

2.4 Neem & ACE Inhibition

Neem is also known to possess ACE inhibition properties, researchers have proven that Neem leaves & Seed extract can be used as potential nutraceutical with antioxidant capacity and inhibitory activity against ACE. (19) (20)

In addition all these Neem is known to reduce Blood pressure (21) (22) And it also used in the treatment of pulmonary inflammation (23) .Neem is known to have anti-depressant effects as it increases the level of serotonin which is responsible for controlling anxiety in humans (24)

3. Neem against COVID-19

Neem leaves are known to have 100+ compounds. (25) An in-silico study has shown that nearly 20+ compounds in Neem leaves show high inhibition against COVID-19 Main Protease (6LU7) with values ranging from -14.3 kcal/mol to a minimum of -9.1 kcal/mol and in-addition to those

compounds there are other compounds from Neem leaves which exhibits medium binding affinity with COVID-19 Main Protease (6LU7). (26)

And in addition to that Neem is effective for its anti-viral properties and it's known to inhibit viruses at any early stage. (11) and also, it's an immunomodulator. All these properties of Neem make it as an ideal choice to inhibit COVID-19 as it can inhibit virus at any early stage and also Neem leaves can control the “over response” of immune system due to which many COVID-19 deaths occur. (27)

Neem leaves have shown to exhibit toxicity only at a level of 0.6g/kg of body weight and the amount of leaves that can be ingested varies depending upon the body weight of the patient. And for any patient up to 10g might be a safe limit when taken over different doses during a day. (28)

4.Case Presentation:

4.1 Patient Information:

The 6 patients were from in the age group 5 to 70 and all of them tested positive for COVID19 and had typical COVID19 symptoms like bodyache, cough, fever etc., Out of the 6 patients ,2 were children and they aged 5 and 13 respectively and others were adult in the age group 36-40 and one was in 60-70 age group, Out of the entire group, 3 were male and 3 were female. 5 of these patients belonged to the same family. The 6th patient had close contact with 3 people who tested negative after taking “Neem” as prophylactic medicine.

Patient 1:

Patient 1 was a female aged 34 years and has started showing COVID-19 symptoms like bodyache and cough etc., The patient had started showing symptoms even before 1 week she tested positive for COVID-19.

Date	Patient history
------	-----------------

June 27 th	Patient tested Positive for COVID-19 and started taking HCQ tablets along with standard prescribed treatment
June 28 th	Patient started taking Neem leaves as dietary supplement along with standard prescribed medication/treatment. It consisted of 9~10g of Neem leaves mixed with water and taken orally in equal doses over 24 hours for a period of over 5 days
June 29 th	25% Improvement was seen in condition of the patient
June 30 th	50% Improvement was seen in the condition of the patient
July 1 st	Patient got fully recovered clinically and become asymptomatic within 3 days

Patient 2:

Patient 2 was a male aged 40 years and has started showing COVID-19 symptoms like body ache etc., and the patient became asymptomatic only after taking Neem leaves mixture.

Date	Patient history
June 27 th	Patient tested Positive for COVID-19 and started taking HCQ tablets with standard prescribed treatment
June 28 th	Patient started taking Neem leaves as dietary supplement along with other standard prescribed treatment. It consisted of 9~10g of Neem leaves mixed with water and taken orally in equal doses over 24 hours for a period of over 5 days
June 30 th	Patient got fully recovered clinically and become asymptomatic within 2 days

Patient 3:

Patient 3 was a female child aged 5 years and had myalgia

Date	Patient history
June 27 th	Patient tested Positive for COVID-19 and was not taking HCQ tablets due to age

June 28 th	Patient started taking Neem leaves as dietary supplement and it consisted of 1~2g of Neem leaves mixed with water and taken orally in equal doses over 24 hours for a period of over 5 days (due to her age Neem doses were smaller)
June 29 th	Patient got fully recovered clinically and become asymptomatic

All the above patients continued to take Neem leaves as dietary for the remaining prescribed period even though they became asymptomatic within 2~3 days of taking Neem.

Patient 4 & Patient 5

Patient 4 was a male aged 37 years and Patient 5 was a male aged 13 years. Both of them were asymptomatic but tested positive for COVID-19. They were prescribed about 4~5g of Neem leaves per day from June 28th and after that they have not become symptomatic even though all of them were in close contact with one another as they are from the same family and were living within the same house.

Patient 6:

Patient 6 was a 69 year old female who was admitted on July 3th. The patient showed some serious illness and her D-Dimer was above 2000 ng/mL. Her lungs showed evidence of old interstitial disease in HRCT and her HB was 9.4 She also had high C-Reactive Protein. Her SpO2 was falling.

Date	Patient history
July 3rd	Patient admitted to Hospital on July 3 rd
July 5th	Patient tested Positive for COVID-19 and was given prescribed treatment. Patient showed some serious illness and her D-Dimer was 2254.55 ng/mL. Her spO2 level has started falling and was given O2.
July 6 th ~ July 9 th	Patient started taking Neem leaves as dietary supplement in addition to the other standard prescribed treatment and was given 9~10g of Neem leaves mixed with water in equal doses for each day for the next 4 days
July 9 th	SpO2 maintained without O2
July 10 th	Patient got recovered clinically. Patient was stable & asymptomatic.
July 13 th	Patient tested negative

Patient 7,8 & 9:

These patients were in close contact of the patient “6” and took Neem leaves as prophylactic medication 3 days before the test was conducted and all of them tested negative on “July 6th”

The treatment given above correlates with principles of “Jwara Chikitsa” in Ayurveda. In Jwara Chikitsa and presymptoms (purvarooopa) of Jwara. “Tikta Rasa” is advised as first line of treatment. Neem is a medicine of “Tikta Rasa”. Nimba is Vishahara and purifier of blood as per Ayurveda. Reference about it in “Charak Samhita Jwara Chikitsa”

“लघ्नं स्वेदनं कालो यवाग्व स्तीक्तको रसः ।

Conclusion:

This case study clearly proves that Neem leaves as dietary supplement can inhibit COVID-19. The 5-year-old female child was not taking any other medicines but was taking about 0.8~1g of Neem leaves and got completely recovered of myalgia within a day and the other 3 patients also recovered quickly within 3~4 days of taking Neem as a dietary supplement along with HCQ & other prescribed treatment. They were previously taking HCQ tablets but as research has shown it alone had no effect within a short period of time and we can only hypothesize that after taking Neem leaves mixture as a dietary supplement they started showing remarkable improvements within 2~3 days and other 2 asymptomatic patients also didn't show any signs or symptoms, which proves that Neem leaves can be used as prophylactic medication also. Since Neem is non-toxic up to 0.6g/Kg of body weight, Neem leaves can be taken in doses over a period of time and all these patients had doses of less than 10g each day with doses spread over as their bodyweight was in the range of 65~81kg which is well within the limits of Neem's toxicity. Also the patients didn't become critically ill due to anti-viral properties of Neem which inhibited the virus within affected cells and prevented it from spreading to other cells within the body. Unlike other drugs Neem doesn't have any side effects unless taken over a long period of time and also orally available which makes it easily available for common people. Neem leaves as a dietary supplement presents a huge opportunity for the Government, Organizations and others to put an end to this pandemic as it can be taken both as prophylactic medicine and also in inhibition of COVID-19 along with other prescribed line of treatment. And effect of Neem leaves a dietary supplement should be further studied with in-vivo and in-vitro studies as the above case study suggests that it does have some effect on COVID-19 with other prescribed treatment.

References

1. **Kumar, Venugopalan Santhosh.** Neem (*Azadirachta indica*): Prehistory to contemporary medicinal uses to humankind. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3695574/> [Online]
2. **A U Mbah 1, I J Udeinya, E N Shu, C P Chijioke, T Nubila, F Udeinya, Angela Muobuikwe, Ancila Mmuobieri, Maria S Obioma.** Fractionated Neem Leaf Extract Is Safe and Increases CD4+ Cell Levels in HIV/AIDS Patients. [Online] August 2007. <https://doi.org/10.1097/mjt.0b013e3180a72199>
3. **I.J. Udeinya, A.U. Mbah, C.P. Chijioke, E.N. Shu.** An antimalarial extract from neem leaves is antiretroviral. [Online] <https://doi.org/10.1016/j.trstmh.2003.10.016>
4. **Vaibhav Tiwari, Nissar A. Darmani, Beatrice Y. J. T. Yue and Deepak Shukla.** In vitro antiviral activity of neem (*Azadirachta indica* L.) bark extract against herpes simplex virus type-1 infection. [Online] <https://dx.doi.org/10.1002%2Fptr.3085>
5. **M M Parida 1, C Upadhyay, G Pandya, A M Jana.** Inhibitory Potential of Neem (*Azadirachta Indica* Juss) Leaves on Dengue Virus type-2 Replication. [Online] Feb 2002. [https://doi.org/10.1016/s0378-8741\(01\)00395-6](https://doi.org/10.1016/s0378-8741(01)00395-6)
6. **Firda Yanuar Pradani¹, Mutiara Widawati¹ and Siwi Pramutama Mars Wijayanti².** Uncovering Potential of Neem and Pyrethrum Extract as Biolarvacide of *Aedes aegypti* for Dengue Control. [Online] January 2007. <https://iopscience.iop.org/article/10.1088/1755-1315/406/1/012007>
7. **A B Reddy, M S Sethi.** Antiviral Effect of Some Indigenous Plant Extracts on Vaccinia & Fowl-Pox Viruses in Chick Embryo Fibroblast Cell Culture. [Online] Nov 1974. <https://pubmed.ncbi.nlm.nih.gov/4377141/>
8. **Badam L, Joshi SP, Bedekar SS.** 'In vitro' antiviral activity of neem (*Azadirachta indica*. A. Juss) leaf extract against group B coxsackieviruses. [Online] June 1999. <https://europepmc.org/article/med/10810594>
9. **Zeinab Nazarian Samani, Mahmoud Rafieian Kopaei.** EFFECTIVE MEDICINAL PLANTS IN TREATING HEPATITIS B. [Online] <https://ijpsr.com/bft-article/effective-medicinal-plants-in-treating-hepatitis-b>
10. **Rukhsana Sher, Tehseen Abaid, Muhammad Zahid and Arshad Kamal Butt.** Evidence of effectiveness of *Azadirachta indica* leaves in chronic hepatitis C in addition of conventional therapy failure. [Online] December 2018. <https://annalskemu.org/journal/index.php/annals/article/view/2630>
11. **Neem, National Research Council (US) Panel on.** Neem: A Tree For Solving Global Problems. <https://www.ncbi.nlm.nih.gov/books/NBK234637/#ddd00096> [Online] 1992.
12. **Marc Schumacher, Claudia Cerella, Simone Reuter, Mario Dicato, and Marc Diederich** corresponding author. Anti-inflammatory, pro-apoptotic, and anti-proliferative effects of a methanolic neem (*Azadirachta indica*) leaf extract are mediated via modulation of the nuclear factor- κ B pathway. [Online] <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3092905/>
13. **Abu Syed Md. Mosaddek, Md. Mamun Ur Rashid.** A comparative study of the anti-inflammatory effect of aqueous extract of neem leaf and dexamethasone. [Online] <https://doi.org/10.3329/bjp.v3i1.836>

14. **J Beuth 1, H Schneider, H L Ko.** Enhancement of Immune Responses to Neem Leaf Extract (*Azadirachta indica*) Correlates With Antineoplastic Activity in BALB/c-mice. [Online] <https://pubmed.ncbi.nlm.nih.gov/16634526/>
15. **Abhishek S. Shah, Mahendra A. Gunjal, Archana R. Juvekar*.** Immunomostimulatory activity of aqueous extract of *Azadirachta indica* flowers on specific. [Online] 2009. <http://www.informaticsjournals.com/index.php/jnr/article/download/218/218>
16. **Alzohairy, Mohammad A.** Therapeutics Role of *Azadirachta indica* (Neem) and Their Active Constituents in Diseases Prevention and Treatment. [Online] March 2016 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4791507/>
17. **Menakshi Bhat, Sandeepkumar K. Kothiwale, Amruta R. Tirmale, Shobha Y. Bhargava and Bimba N. Joshi.** Antidiabetic Properties of *Azadirachta indica* and *Bougainvillea spectabilis*: In Vivo Studies in Murine Diabetes Model. [Online] November 2011. <https://www.hindawi.com/journals/ecam/2011/561625/>
18. **KN Bopanna, J Kannan, Gadgil Sushma, R Balaraman, SP Rathod.** Antidiabetic and antihyperlipaemic effects of neem seed kernel powder on alloxan diabetic rabbits. [Online] March 1997. <http://www.ijp-online.com/article.asp?issn=0253-7613;year=1997;volume=29;issue=3;spage=162;epage=167;aulast=Bopanna;type=0>.
19. **Arise, Rotimi O.** Kinetics of angiotensin -1 converting enzyme inhibition and antioxidative properties of *Azadirachta indica* seed protein hydrolysates. [Online] May 2019. <https://dx.doi.org/10.1016%2Fj.heliyon.2019.e01747>
20. **Siddhesha, Cletus and B S Vishwanath.** Inhibition of Angiotensin Converting Enzyme(ACE) by Medicinal Plants Exhibiting Antihypertensive Activity. [Online] March 2010. https://www.researchgate.net/publication/303693276_Inhibition_of_Angiotensin_Converting_Enzyme_ACE_by_medicinal_plants_exhibiting_antihypertensive_activity
21. **Abdul Jabbar Shah, Anwarul-Hassan Gilani, Hashim Muhammad Hanif, Saeed Ahmad, Sana Khalid and Ishfaq A. Bukhari.** Neem (*Azadirachta indica*) Lowers Blood Pressure through a Combination of Ca++ Channel Blocking and Endothelium-Dependent Muscarinic Receptors Activation. [Online] November 2014. <http://dx.doi.org/10.3923/ijp.2014.418.428>
22. **Idongesit Obiefuna, Ronald Young.** Concurrent Administration of Aqueous *Azadirachta indica* (Neem) Leaf Extract With DOCA-salt Prevents the Development of Hypertension and Accompanying Electrocardiogram Changes in the Rat. [Online] September 2005. <https://doi.org/10.1002/ptr.1739>
23. **Jae-Won Lee, Hyung Won Ryu.** Protective effects of neem (*Azadirachta indica* A. Juss.) leaf extract against cigarette smoke- and lipopolysaccharide-induced pulmonary inflammation. [Online] October 2017. <https://www.spandidos-publications.com/10.3892/ijmm.2017.3178>
24. **Conrick, John.** Neem the ultimate herb. [Online] https://books.google.co.in/books?id=Q-0a6SXDKB0C&pg=PA49&lpg=PA49&dq=increase+in+serotonin+causes+Neem&source=bl&ots=m1Br_X26qu&sig=ACfU3U0KTCQ9I2ckPyGoBSYB02KyViegjA&hl=en&sa=X&ved=2ahUKEwiDnvSa8LjqAhUwyzgGHQRuCSYQ6AEwDXoECAkQAQ#v=onepage&q=%20serotonin&

25. **All the constituents of Neem leaves.** [Online] <http://www.neemguide.com/all-the-constituents-of-neem-leaves/>.

26. **Subramanian, Shanmuga.** Nearly 20+ compounds in Neem leaves extract exhibit high binding affinity with some of them as high as -14.3 kcal/mol against COVID-19 Main Protease (Mpro) : A Molecular Docking Study. [Online] April 2020. <https://doi.org/10.35543/osf.io/pyqx4>

27. **XinjuanSun.** Cytokine storm intervention in the early stages of COVID-19 pneumonia. [Online] 2020 June. <https://doi.org/10.1016/j.cytogfr.2020.04.002>

28. **S, Pingale Shirish.** Hepaprotection study of leaves powder of Azadirachta Indica A.JUSS. [Online] August 2010. <http://www.globalresearchonline.net/journalcontents/Volume3issue2/Article%20007.pdf>