Chapter 8

Repurposed antibiotics and phytochemicals for therapeutic efficiency in neurotropic viral infection

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8. Repurposed antibiotics and phytochemicals for therapeutic intervention in neurotropic viral infection

Literature review, hypothesis and work plan:

8.1 Repurposed antibiotics and phytochemicals in Central Nervous System viral infection

Plant-derived phytochemicals are diversified bioactive compounds having various classes, such as terpenoids, flavonoids, alkaloids, and phenols, some of which are used variously as investigational therapeutic agents in neurological disorders. Podophyllotoxin is an aryltetralin-type lignan isolated from perennial herb *Podophyllum hexandrum* that shows comparable potency with the tetracycline class of antibiotics [158]. Furthermore, chlorogenic acid obtained from plants, such as *Andrographis paniculata*, *Bixaorellana*, *Gardenia resinifera*, *Pongamia pinnata*, *Sphaeranthus indicus*, *Solanum trilobatum*, *Soyamida febrifuga*, and *Thespesia populnea*, belongs to the hydroxycinnamic acid family, and contains caffeic acid and quinic acid, which are reported to have comparable antibacterial, antiviral activity [159], and significant β-lactamase inhibitory activity as cephalosporin [160]. Naringenin[161] and quercetin [162] are the other potent phytochemicals, predominantly present in *Pongamia pinnata*, *Thespesia populnea*, *Andrographis paniculata*, *Psoralea corylifolia*, *Soyamida febrifuga*; these phytochemicals also possess an essential anti-inflammatory role.

8.2 Rationale of using phytochemicals as therapeutic intervention

Phytochemicals possessing therapeutic potentials are complex by nature; their potency manifests by targeting multiple targets via different phytoconstituents. Therefore, we have taken the network pharmacology approach to investigate the explicit mechanism of phytochemicals for their efficacy in CNS infection. This approach also includes the

polypharmacology framework, which helps us replace the customary “one-drug/one-target” model with a “multidrug/multitarget” model. Here, we have found the common targets for the phytochemicals with respect to viral infections (Japanese Encephalitis and COVID-19) so as to identify how aiming at multiple targets can cause an efficacious remediation in the disease process.

Moreover, most of the antimicrobial therapeutic agents used to treat CNS infection require prolonged treatment due to their poor penetrability to CNS, which causes several adverse effects and side effects. Phytochemicals obtained from medicinal plants possess several neuroprotective properties due to their efficient blood brain barrier (BBB) permeability. In this study, a phytochemical of interest, chlorogenic acid, is reported to have significant brain uptake after intravenous and intranasal administration. They have found that the concentration of chlorogenic acid in the brain is higher in intranasal administration compared to IV administration. [163]. Naringenin and its glucuronides (metabolites of naringin) exhibited the ability to permeate the BBB into the brain as it has log P value of 2.3 which is within the acceptable threshold of 1.5–2.7 for a BBB permeable substance [164]. Ishisaka et al. reported satisfactory BBB permeability of quercetin through an in vitro study with the rat brain capillary endothelial cell line [165]. Additionally, the highly lipophillic tetracycline class of antibiotics also easily penetrates BBB [166, 167].

8.3 Predicted pathway for virus transmission

To underscore, our study is the first human report (as far as we know) to show the following two connections: (i) linkage between gustatory nerves and the respiratory center (ii) linkage between the olfactory nerve and the limbic system areas, and these two connections are demarcated via deterministic tracking with MRI fiber tractography so as to provide neuroanatomical validation in human subject. These two connected routes can provide the anatomical basis by which viral migration can occur in human retrogradely to

the brain from: (a) the nasal and buccal routes (for virus lodged in the mouth and the nose from oral input), and (b) the vagal route (for virus reaching the lungs from inspired air).

8.4 Hypothesis and Framework of the Investigation

We developed a quantitative basis of the activity of our proposed drugs on virus and the host cell, analysed the framework for further enhancement, and developed a predictive platform to identify the newer drugs that would be effective for COVID-19 and similar acute neuro-respiratory/neuro-inflammatory viral infections. Our approach is validated by findings from human clinical trials [29]. Thus, we can consider the drug-receptor interaction to have two components: drug-virus interaction and drug-host cell receptor interaction. Accordingly, our present investigation aims to study the effect of phytochemicals in viral-mediated neuro infections. Therefore, the current study was designed to identify the neuroanatomical pathways through which the virus can cause CNS migration and infection, as well as to examine the specificity and potency of proposed therapeutic phytoconstituents by performing structural biology-based docking studies. Thereby, we identified the predominant mechanisms through which phytochemicals can show therapeutic efficacy using network pharmacology approach. A quantitative model is also developed to determine the virostatic potency and the virucidal potency (Figure 44). Our bioinformatics studies demonstrated that phytochemicals and the tetracycline class of antibiotics, (especially the newer class flurocycline and glycylcycline, and the standard drug minocycline), have a binding affinity towards: (1) the main protease of COVID-19, and (2) the binding site of angiotensin-converting enzyme 2 (ACE2) receptor where the SARS-COV2 viral spike receptor binds. Similarly, the binding affinity of these drugs and phytochemicals with NS3 helicase/nucleoside triphosphatase of Japanese encephalitis is also evaluated. We also assessed the binding affinity of ceftriaxone (cephalosporin) toward these receptors.

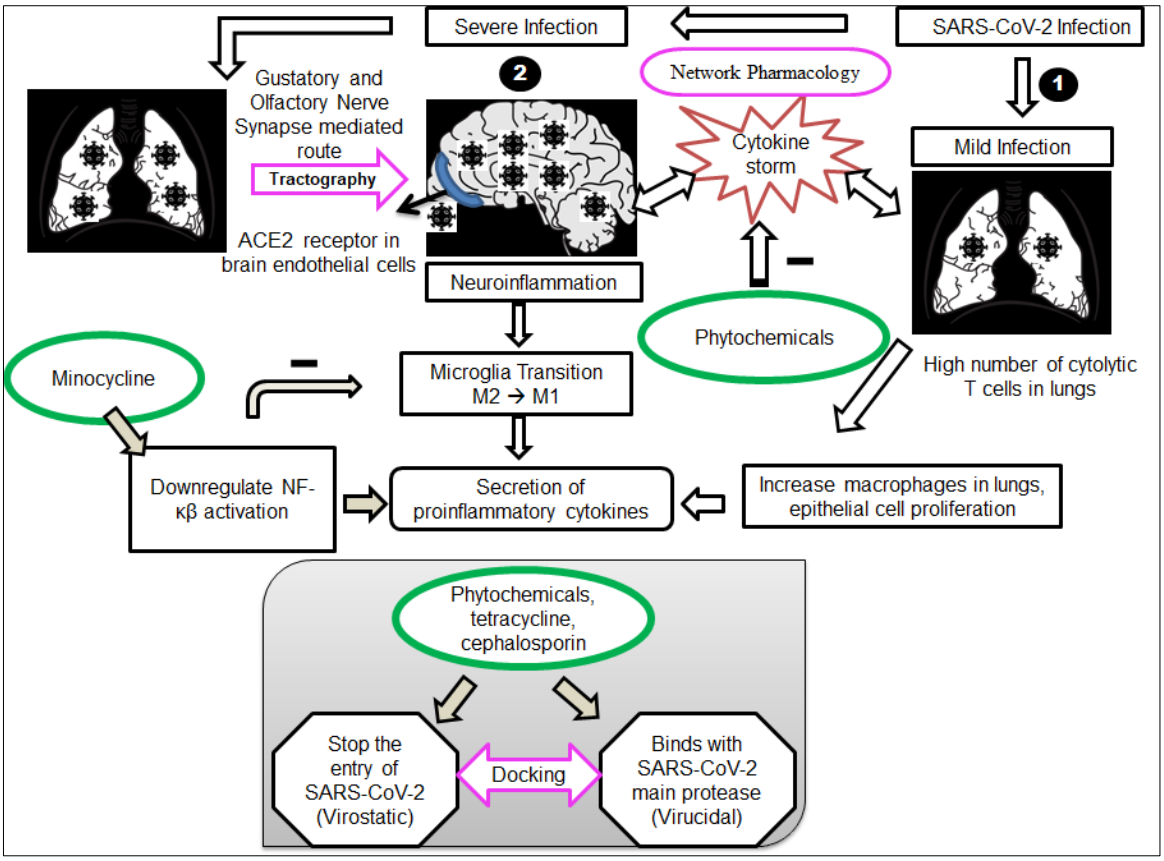

Figure 44: *Cell signaling pathways during mild and severe infections with SARS-COV2 and proposed therapeutic intervention of phytochemicals, tetracycline and cephalosporin ligands. (1) Mild infection with SARS-COV2, mainly lungs get affected, causing a high number of cytolytic T cells in the lungs. Phytochemicals act by targeting the T cells and monocytes, driving the cytokine storm in patients, leading to neuroinflammation. (2) Severe infection with SARS-COV2, affecting both lungs and the brain. Virus transmitting through a gustatory and olfactory nerve (tractography)-mediated route, causing neuroinflammation alleviated by Minocycline. Docking studies of phytochemicals, tetracycline and cephalosporin ligands, with the SARS-COV2 spike receptor-binding domain and main protease verify our approach.*

8.5 Our mathematical formulation of system analysis: Double hit model

We have developed two-stage approach for virus physiology, (i) drug-virus receptor interaction and (ii) drug-host cell receptor interaction. Two different drugs can attack the two stages, or a single drug can target both stages.

Model Quantitative Developement: At the initial time t = 0, let there be N_0 receptors, of which N_C is the number of receptors in the host cells; these receptors are the host cell receptors through which the viral material enters (this receptor can also be occupied by a drug, preventing the entry of the virus). Likewise, N_V is the number of receptors in the viral wall, and if the drug molecule approaches, it can damage the virus. The total number of receptors *(N)* on which the drugs can actis thus $N = N_C + N_V$. If N is normalized to 1, then the N_C and N_V can be expressed as a fraction.

$$N_C/N + N_V/N = N/N = 1; \qquad (1)$$

that is, ${}^nC_0 + {}^nV_0 = 1$

where ${}^nC_0$ and ${}^nV_0$ denote the fractional population of the receptors in the virus and the host cell respectively, at time t = 0.

Thus, pharmacological action against the virus can be at two sites: (i) the virus coat/virus genome, where the drug damages the virus or, (ii) the host cell receptor, where the drug prevents virus entry. In such condition, at the initial time t_0, drug action starts on. However, as time elapses, dissipating processes will happen, leading to first-order decay in the efficacy of the drug-receptor interaction. The well-known process of cytotolerance occurs due to increasing efflux and ejection of the drug from the cell receptors or virus receptors. Hence, as time ensues, the time-varying fractional population of cell receptor ${}^nC$ (t_1) would decrease in the first-order or exponential mode as

$$ {}^nC(t) = {}^nC_0 \times e^{-\alpha t} \qquad (2)$$

Likewise, the fractional population of the virus receptor would decrease as:

$$^{n}V(t) = {}^{n}V_0 \times e^{-\beta t} \qquad (3)$$

The combined fractional population of both receptors as time elapses would be:

$$n(t) = {}^{n}C(t) + {}^{n}V(t) = {}^{n}C_0 \times e^{-\alpha t} + {}^{n}V_0 \times e^{-\beta t} \qquad (4)$$

At the initial time t = 0, the aforesaid equation becomes

$$^{n}C_0 + {}^{n}V_0 = 1 \qquad (5)$$

Equation (5) may be compared with equation (1). We have plotted an illustrative curve of Equation 4 (Figure 45, Drug A). As the number of viruses is more diminutive than cells, we can take as an instance the fractional virus receptor population, $^{n}V = 0.25$, and fractional cell receptor population $^{n}C = 0.75$. Different drugs can interact differentially on the receptor; one drug may be more effective on the cell receptor. Thus, the viral receptor and relative tolerance of the receptor to the drugs can vary, i.e., all the terms $^{n}C_0$, $^{n}V_0$, α, and β can vary according to the drugs. We show the curves of two drugs (A and B) with different receptor activities (Figure 45).

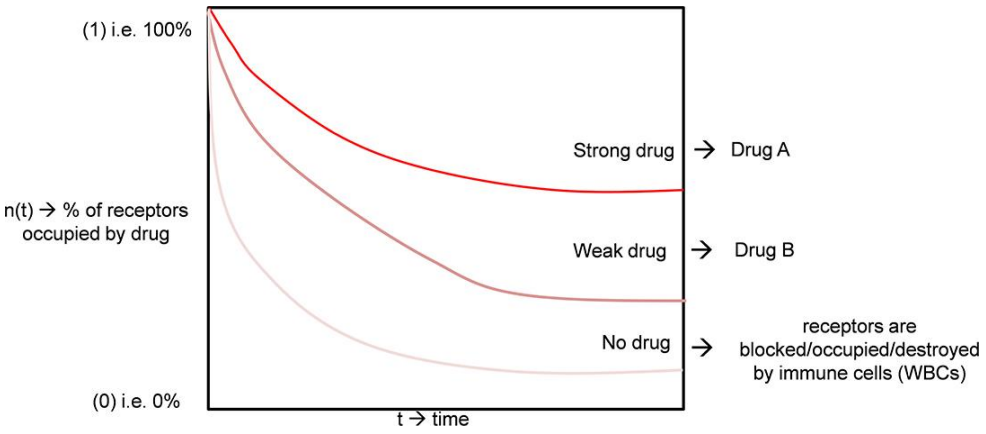

Figure 45: *The quantitative model of drug interaction with a viral receptor based on its potency*