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Review Article

Model of Anti-Covid-19 Pharmacon

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ABSTRACT

COVID-19 pandemic opens multiple opportunities for innovations in the drug –design. Combinational therapeutics and renewal of orphan drugs as antivirals. The drugs of pharmacological diversity may be tomorrow of viral replication blockers. A model of polyactive pharmacon is suggested for hybridizing structural moieties of virucidal relevance.

Keywords: COVID-19, Pharmacon, Biocompatible, Vunerable, Virucidial.

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INTRODUCTION

COVID-19 is novel virus appeared in 2019[1-2]. It has intricate self-replicating machinery and is positive sense single stranded RNA virus. COVID-19 has four major structural proteins – Spike, envelope, membrane and nucelocapsid. It needs protease M^{pro} or $3Cl^{pro}$ for forming viral-replicase complex and use ACE-2 (Angiotensin converting enzyme-2), concentrated in epithelium cells of host. ACE-2 receptor facilities encapsulation of viral capsid.

The genomic RNA after infection is released into cytoplasm of host cells and translated into overlapping poly-proteins, processed by M^{pro} like protease. This produces multiple functional proteins that are essential for viral replication.

Theoretical methodology

There are two ways to fight back COVID-19 by 3D complementariness of drugs.

- Drugs attack virus proteins preventing them to enter host cell or copying their genetic material.
- Drugs block interaction of viral protein with host protein (host matching).

The virustatic mortality is reversible whereas virucidial is irreversible[3]. Both follow the extracellular mechanism for blocking the viral entry to the host cells. Virucidal drugs bring the structural changes on viral surface for prohibiting viral entry. Antivirals terminate the viral ability to replicate.

Anti-COVID-19 medications have versatile chemical pharmacology – ranging from anti- malarial, anti-HIV, anti-parasitic, anti-influenza, anti-bronchitis, anti-arthritis, anti-pneumonia and ACE-2 antagonists.

Notably –Remdesivir[4-5], Azithromycin6[-7], Chloroquine, Hydroxy chloroquine are potential inhibitors of SARS-COV-$2M^{pro}$, SARS-COV-$3Cl^{pro}$ and NSPIZ RNA polymerase.

Chloroquine and Hydroxychloroquine are weak bases. The viral entry into host cells by endocytosis require acid pH in endosomal vesicle for viral - host fusion so carry out replication process. Both basic drugs increase the pH and impair replication by blocking the viral entry. Umifenovir[8] also blocks viral fusion with target membrane for entry into host cell. This process needs the kinase activity. Arbidol acts as an inhibitor of AbI kinase. Favipiravir[8] is selective inhibitor of viral RNA dependent polymerase. The virucidal action of some of them blocks interleukin-6-receptor release interferons and suppress TNF_2 activity for curbing viral inflammation.

Azithromycin is macrolide antibiotic. It interfere with protein synthesis by binding to 50S ribosomal subunit of bacterial ribosome, thus inhibits translation of m-RNA.

Remdesivir is prodrug of ribonucleotide analog. It enters infected cells where converted into monophate by action of

esterase / phosphoramidases. This is further phosphorylated to active tri-phosphorylatedmetabolite by nucleoside phosphate kinases which interfere with action of viral RNA dependent polymerase thereby decrease in RNA production occurs and induce irreversible chain termination. Actually remdesivir is delayed chain terminator.

Ribavirin[9] is synthetic prodrug of guanosine analog, having triazoyl and carboxamide functionalities. The broad spectrum activity lacks viral specificity. The provisional RNA specificity blocks viral RNA synthesis and viral m RNA capping. All these mode of actions were studied to search virudical functionalities in these diversified antivirals.

We studied the chemical structures of Chloroquine, Hydroxychloroquine, Favipiravir (Avigan), Umifenovir (Arbidol), Ribavirin, Remdesivir and Azithromycin. They are all broad spectrum antivirals. Their selection led us to model Anti-COVID-19 polyactive pharmacon which may probably analogous to pharmacophore.

DISCUSSION AND RESULTS

Pharmacon[10] represents biological activeness including endogenous compounds and drugs. Medically it is related to pharmacological agonists and antagonists.

We re-innovated this definition: Pharmacon is biocompatible medication which may be mono active (monotherapy – specific action selective) or poly active (combination therapy-nonspecific - nonselective).

A model of anti-COVID-19 pharmacon is derived from the vunerable virucidial functionalities of prescriptive viability. The mechanism of diversified antivirals helped to identify such structural moieties. Their antiviral rationality is briefed further:

- Chloroquine (pka_1=8.4, pka_2=10.18)and hydroxychloroquine (pka_1=7.1, pka_2=8.1). Basic territory nitrogen and pka values change acidic pH for blocking viral entry.
- Favipiravir (Avigan) shows keto-enol type tautomerism. This impart optimal acidity for anti-inflammatory action against viral-inflammation.
- Umifenovir (Arbidol): It has partial structural resemblance with indomethacin. Supposedly it has balanced pH (COOH, phenolic dimethyl amino group) for inhibiting viral fusion. Further hydrophobic aromatic stacking interactions with tyrosine and tryptophan of viral glycoproteins has direct antiviral action.
- Remdesivir and Ribavirin: The phosphorylation of D-ribose hydroxyls produce bioactive triphosphorylated metabolites for blocking viral replication.
- Azithromycin: The macrolide structure has strong hydrophocity (13-methyl groups) and less hydroxyls which act as H-donors and acceptors.

- A model of anti-COVID-19 pharmacon should meet the three criterions

- The blocking of viral entry and viral inflammation requires delicate balance of weak basicity and moderate acidity.
- The termination of viral; replication needs bioactive phosphorylation of hydroxyls.
- Hydrophobic and H-bonding are essential for interaction with viral receptor.

CONCLUSION

The extrinsic inhibition of viral infectivity is the best option for the public health.Anti-COVID-19 modeling of pharmacon has disruptive approach for the irreversible damage to viral entry. The designing of new antivirals should search new biosteric virucidial groups for better chemotherapy.The concept of poly active pharmacon implies the addition of antimutagen and immunodulator in combinational therapeutics regimen/protocol. To improve delivery system, nano particals of virucidial drugs can be preferred as they become nontoxic and broad spectral.

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