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Organic Structure & Function of Anti Covid Drugs Along with Development of Covid Vaccine in India

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ABSTRACT: Coronaviruses, named for their “sun-like” shape observed in the electron microscope, use RNA molecules to encode their genes, as do influenza viruses, HIV, and rhinoviruses (common cold). SARS-CoV-2, the virus that causes COVID-19, infects mammals and birds. It is closely related to the viruses causing the earlier SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome) outbreaks.

The coronavirus particles are organized with long RNA polymers tightly packed into the center of the particle, and surrounded by a protective capsid, which is a lattice of repeated protein molecules referred to as coat or capsid proteins. In coronavirus, these proteins are called nucleocapsid (N). The coronavirus core particle is further surrounded by an outer membrane envelope made of lipids (fats) with proteins inserted. These membranes derive from the cells in which the virus was last assembled but are modified to contain specific viral proteins, including the spike (S), membrane (M), and envelope (E) proteins. At present a crore population death is due to corona in India. Many treatments have been tried and therapies done to defend and they have worked too. Now vaccine development has been done to prevent corona disease.

I. INTRODUCTION

For treatment drugs, selected methods of computational chemistry, the strategy of integrative structural modification of small-molecules with antiviral activity into potential active complex molecules has been presented. Proposed molecules have been designed based on the structure of triterpene oleanolic acid and complemented by structures characteristic of selected anti-COVID therapy assisted drugs. Potential drugs, in addition to high-molecular forms containing peptide or antibody units, include so-called ‘small-molecule chemicals’, characterized by the ability to interact with any of the key enzymes implicated in the development of this pathogen. High hopes are also being placed on the use of plasma from people who have recovered from COVID-19 and are capable of producing appropriate antibodies to attack the virus. These antibodies, following appropriate isolation process, can be incorporated into treatment as a specific therapeutic agent. Most of these entities have already been used, with a greater or lesser degree of therapeutic success, as drugs with primarily antiviral activity. The group also includes antibacterial, antimalarial and antiparasitic agents, and other drugs.[1]

In this context, immense importance has been given to the so-called drug repurposing, which involves the identification of new areas of application and use for well-known and widely used chemical molecules. In their study, based on bioinformatics analysis and generated networks of functional drug–gene interactions, the authors identified 16 well-known but especially promising substances with different recognized primary indications and, in each case, with concurrent antiviral properties. They include irbesartan, toremifene, camphor, equilin, mesalazine, mercaptopurine, paroxetine, sirolimus, carvedilol, colchicine, dactinomycin, melatonin, quinacrine, eplerenon, emodin and oxymetholone.

Furthermore, the authors suggested that a potentially significant therapeutic effect can be achieved by combining two drugs for concurrent administration. Such potential pairs include sirolimus with dactinomycin, mercaptopurine with melatonin and toremifene with emodin. Among the 43 drugs listed, there are also four antibiotics which have been found to be effective against other coronavirus strains. They include monensin, oritavancin, dalbavancin and teicoplanin, as well as azithromycin. In addition to drugs acting against other viruses, other candidate drugs for the repurposing process discussed here include a number of antibacterial, antifungal, antiprotozoal and antiparasitic (also antimalarial) agents, in other words collectively termed antimicrobial drugs, as well as anthelmintics. Two substances included in the above list, hydroxychloroquine and chloroquine, which have long been used as antimalarial agents,

were among the first to be selected as drugs with a potential to fight SARS-CoV-2. However, it was quickly found that the drugs had to be used at significantly higher doses than in the traditional indications in order to observe an improvement in COVID-19 patients. [2]

Table 1: Existing therapeutic agents which have been considered as candidate drugs for the treatment of COVID-19.

Drug name	Chemical group	Already known indications
Tenofovir	Nucleotide analog	Antiviral
Oseltamivir	Polisubstituted cyclohexene	Antiviral, selective neuraminidase inhibitor
Pyrazofurin	Nucleoside analog	Antiviral, antibiotic, anticancer
Disulfiram	Disulfide	To treat alcohol dependence
Irbesartan	Imidazolone derivative	Antihypertensive
Mercaptopurine	Purine derivative	Antimetabolite, antineoplastic
Mesalazine	Aminosalicylic acid	Anti-inflammatory
Toremifene	Stilbene derivative	Antineoplastic
Eplerenone	Synthetic steroid	Diuretic
Paroxetine	Piperidine derivative	Antidepressant
Dactinomycin	Macrolide antibiotic	Antineoplastic, antibiotic
Melatonin	Indole derivative	Hormone
Equilin	Steroid, estrone derivative	Estrogen
Quinacrine	Acridinederivative	Antimalarial
Carvedilol	Carbazole deriv. of amino-2-propanole	Nonselective beta-blocker
Colchicine	Alkaloid	Anti-inflammatory
Camphor	Monoterpene	Antipuritic, antiinfective
Oxymetholone	Steroid	Anabolic
Ebselen (PZ51)	Selenazon	Anti-inflammatory, cytoprotective
Tideglusib	Tiadiazolodion	Anti-Alzheimer's disease
Carmofur (HCFU)	5-Fluorouracil derivative	Anticancer
Shikonin (Alkannin)	Naphtoquinone derivative	Natural red-brown dye
PX-12	Imidazodisulfide	Thioredoxin inhibitor, anticancer
Amoxicillin	Beta-lactam antibiotic	Antibiotic
Azithromycin	Macrolide antibiotic	Antibiotic
Glycyrrhizin	Triterpene saponin	Sweet substance, antiulcerous
Oleanolic acid	Triterpene	-
Ursolic acid	Triterpene	-
Hederagenin	Triterpene	-
Curcumin	Diarylheptanoid	-
Coriandrin	Furoisocoumarin	-
Apigenin	Flavonoid	-
Rosmarinic acid	Phenolic acids ester	-

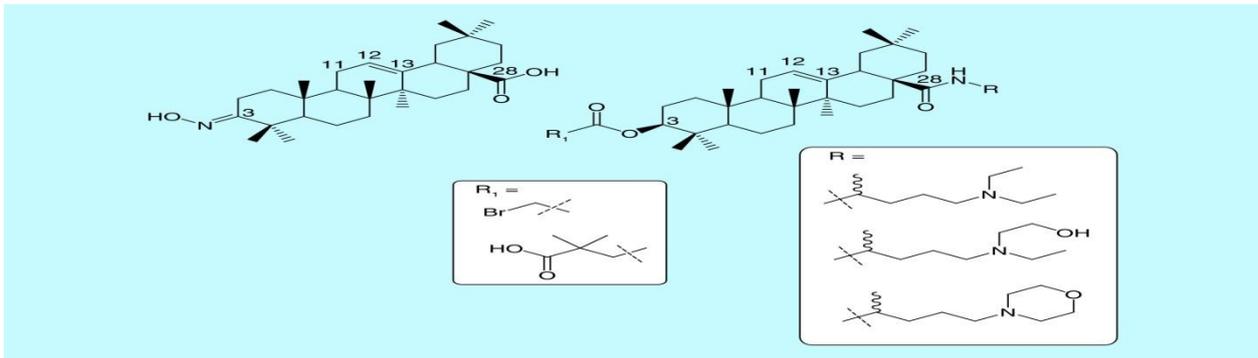


Fig.1: Selected derivatives of oleanolic acid modified at the C-3 and/or C-28 positions, showing a high level of biological activity (including antiviral effects).

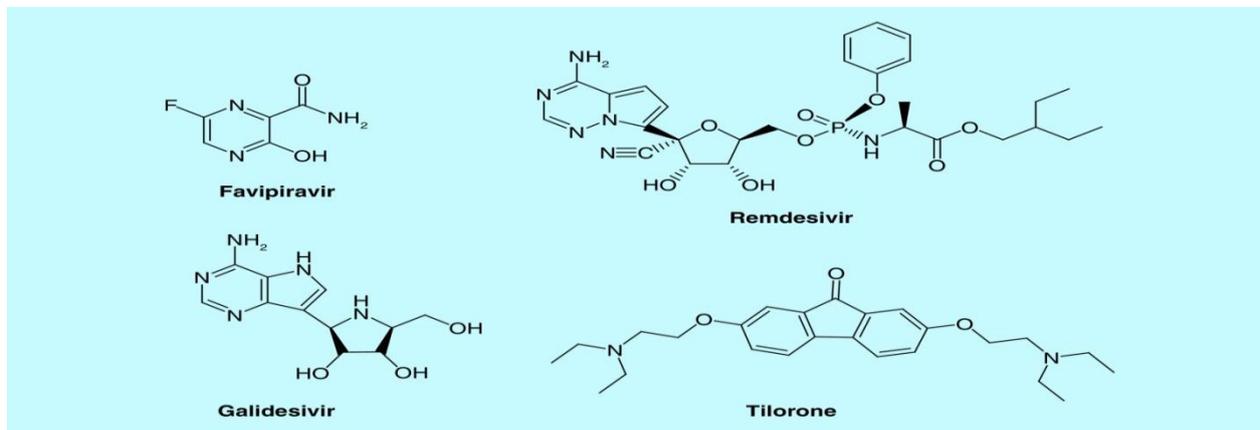


Fig.2: Structure of antiviral drugs proposed for the synthesis of ‘molecular consortia’ with oleanolic acid derivatives potentially exhibiting high activity against SARS-CoV-2.

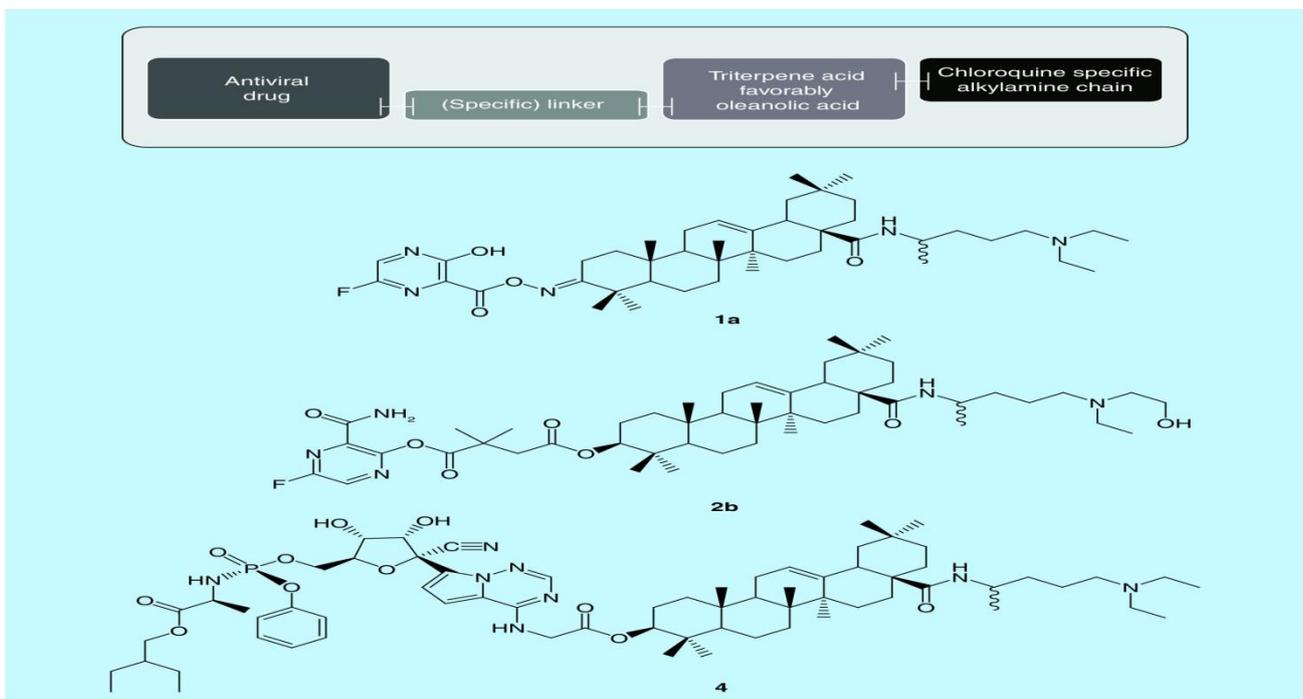


Fig.3: General block diagram and structure of new selected proposed anti-SARS-CoV-2 substances.



The practical application of these concepts and presented calculations will offer an opportunity to obtain new chemical entities which are highly likely to be useful in the fight with the COVID-19 pandemic. It can be noted that much importance in the fight with COVID-19 has been ascribed to the method of repurposing known drugs, especially those with an established activity against the influenza virus and used for the control of other diseases caused by microorganisms or protozoa. Drug repurposing is a method with a great potential which is still far too little used, and it may reveal itself as an extremely effective way of fighting diseases emerging in the future. Another well-proven, widely used and promising tool of modern medical chemistry is the search for completely new entities in the area of so-called small-molecule drugs. In addition, a currently fashionable, though not new, direction in the search for effective drugs involves taking advantage of the pharmacological potential of substances of natural origin.[3]

Antiviral Therapies for Infected Individuals

Addressing the health hazards of coronavirus infections would benefit greatly by anti-viral drugs that act to block the attachment and internalization process or the replication of the virus within infected cells. Antivirals that interfere with the viral lifecycle without significantly impacting normal cellular function are critical to combating viral infections. Such therapies are in use for other RNA viruses, like influenza, and are administered generally as small molecules, taken in pill form. These antivirals act by binding to and interfering with viral proteins needed to replicate the viral RNA or facilitate binding and entry of the virus into the cell. Another class of antiviral drugs, which are effective with HIV, act by interfering with the synthesis and assembly of the coat proteins into the viral capsid. The US pharmaceutical industry already has the capacity to produce millions of doses of small molecules, so the rate limiting step in this case is more likely to be at the laboratory research and development stage. Triterpene compounds, as the basic skeleton, equipped with additional elements of known antiviral (and similar) drugs are currently undergoing intensive studies to determine their suitability for repurposing in COVID-19 therapy. Favipiravir, remdesivir, galidesivir and tilorone as antiviral drugs have been proposed for introduction into the oleanolic acid structure in C-3 position of the triterpene backbone by the hydroxyimino-, acetate- or dimethylsuccinate group as the linker. Alkylamine substituent (derived from the chloroquine molecule or its analogs) have been proposed for attachment via an amide bond at the C-28 position of the triterpene backbone. A combination of the above-mentioned three elements results in 18 designed complex structures with significant antiviral properties offering the greatest prospects for use in COVID-19 therapy. Based on the selected methods of computational chemistry the molecular parameters and the preliminary activity characterizing designed molecules as potential drugs were calculated and predicted. The results of the above analysis show that among the designed complex structures with potential antiviral activity targeting mainly SARS-CoV-2, the highest therapeutic potential is noted for the compounds containing a molecule of favipiravir in addition to the N-alkylaminoalkylamide fragment connected with oleanolic acid. Owing to the presence of fragments of three drug substances with significant antiviral properties incorporated into one molecule, the molecule will be active in at least two different phases of the coronavirus life cycle as a multitargeted drug.[4]

II. VACCINE DEVELOPMENT

Developing a vaccine requires growing large amounts of virus, often in animals, or in tissue culture at large scale. The viruses are inactivated by radiation, heat, or chemicals, or are derived from genetically weakened strains. Another alternative is to purify not the complete virus, but isolated viral proteins like spike. This is safer and easier to scale up, but the immune system response to the isolated protein is often not as robust as it is to the organized lattice of the intact virus particle. A more recent strategy involves injecting individuals with RNA or DNA encoding for viral proteins. These nucleic acids can be administered alone or through man-made vectors that help deliver material into the body. In any strategy, however, enough material is needed to inject reasonable doses into millions of people.[5]

Here are the latest updates on Covid-19 vaccines in India:

- 1) **Pfizer** - The Indian arm of the US drug firm had sought an emergency use approval for its Covid-19 vaccine from the central drug regulator days back after the firm secured such clearance in Britain and Bahrain. The drug giant, in its application, had sought permission to import the vaccine for sale and distribution in India. - Efficacy rate: 95%
- 2) **SII's Covishield** - Pune-based Serum Institute of India has already applied for emergency use authorisation of the vaccine, dubbed as Covishield, in India. SII chief Adar Poonawalla recently said that the company plans to make up to 10 crore doses of Oxford University-AstraZeneca vaccine each month, starting next year. - Efficacy rate: 60-70%
- 3) **Bharat Biotech's Covaxin** - The Hyderabad-based company, earlier this month, sought emergency use approval from the Drug Controller General of India for its indigenously made Covid-19 vaccine Covaxin. Covaxin is being indigenously developed by Bharat Biotech in collaboration with the Indian Council of Medical Research. - Efficacy rate: 60%



4) **India's first mRNA vaccine** - A vaccine being developed by the Gennova firm in Pune has become India's first homemade mRNA candidate to get permission for the human clinical trial. "HGCO19 (the official name of the vaccine) is stable at 2-8 degrees Celsius for two months," the government had said in an official statement.[6,7]

5) **Zydus Cadila** - Zydus Cadila had, earlier this month, received approval from the DCGI to start phase 3 clinical trials with its biological therapy PegiHep in Covid-19 patients. The company had completed phase 2 clinical trials with PegiHep last month.

6) **Sputnik V** - India has purchased 100 million doses of Russia's Sputnik V Covid-19 vaccine candidate. Sputnik V vaccine has been developed by the Gamaleya National Research Center of Epidemiology and Microbiology and Russian Direct Investment Fund (RDIF). Dr Reddy's Laboratories and Sputnik LLC are jointly conducting the human trials in India.[8,9]

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