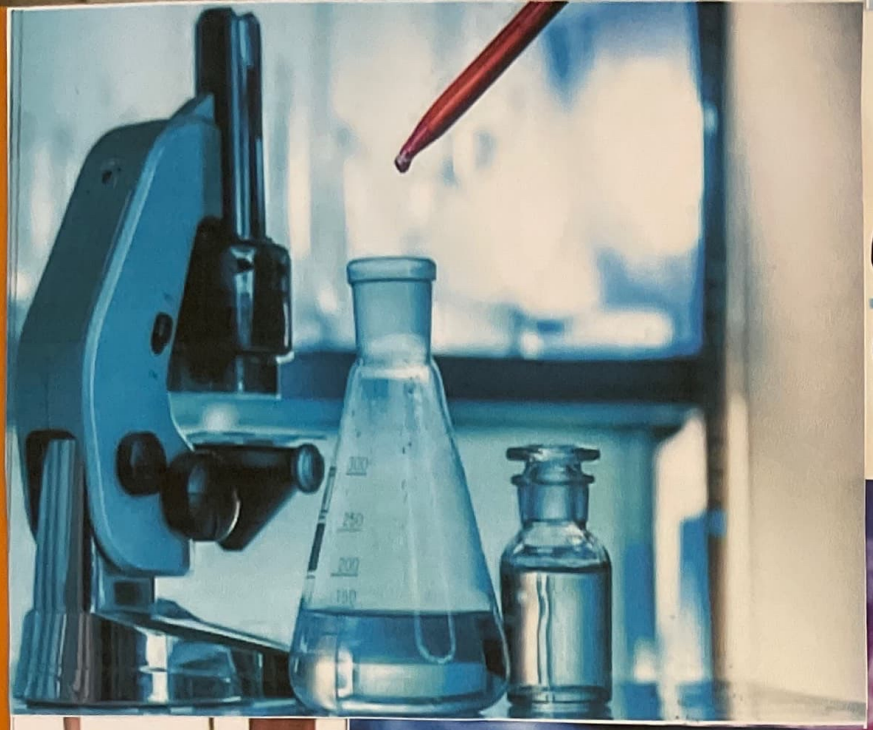


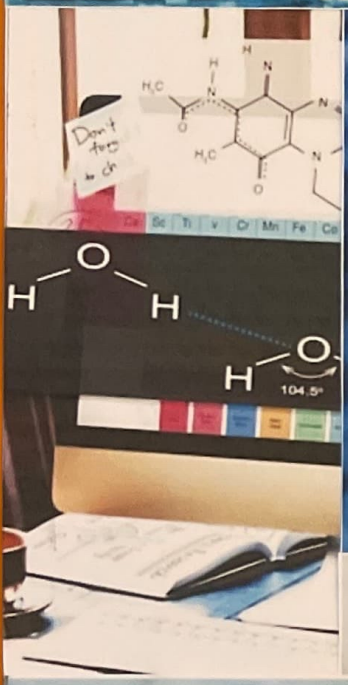
MARIAM HUSAIN

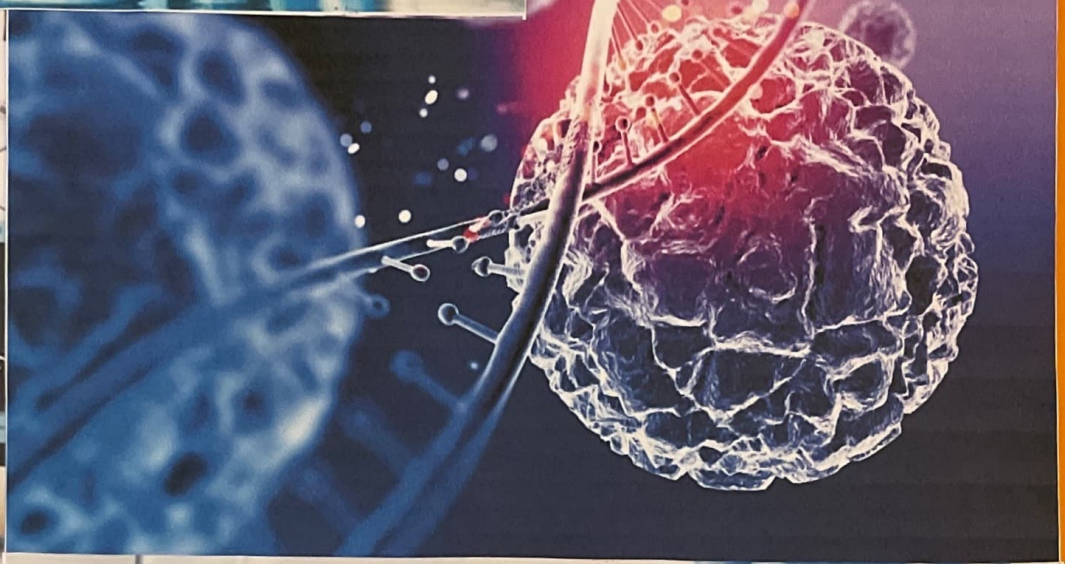
XI/B

Chemistry Vs. COVID

CHEMISTRY project

2022-23





INDEX

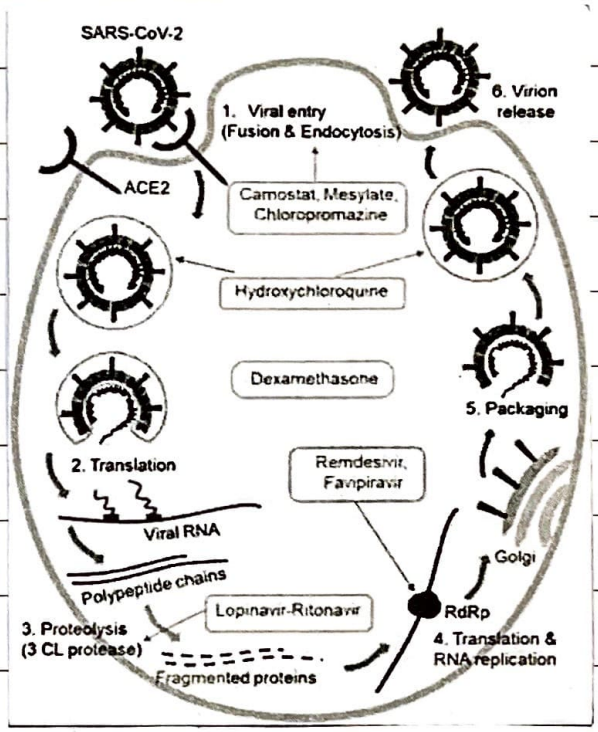
INTRODUCTION

Chemistry plays a key role in understanding viral structures and helps in the development of chemical preventive measures and drugs for COVID-19. A collaborative approach not only between chemists and biomedical researchers, but also an interdisciplinary response among different branches of chemistry community, is essential.

The COVID-19 challenge stands at the intersection of chemistry and biology. COVID-19 is an infectious disease caused by the novel severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). It has developed into a global pandemic, and disrupted society on a previously unimaginable scale. The virus can cause severe disease with pneumonia and acute respiratory stress disorder.

Chemists and biomedical researchers have detected the virus, sequenced its genome and are determining protein structures. Personal preventive measures including chemical preventive measures such as soap water, bleach, alcohol-based sanitizers, and hydrogen peroxide have been conceptualised and prepared to destroy the virus. Advancement of various testing tools, antiviral drugs, vaccines, and other medical developments are being done in a fast paced manner. This may seem outside the scope of chemistry - which tends to deal with elements and compounds - but I would like to demonstrate how biochemistry has a key role to play in understanding viral structure.

MECHANISM OF ACTION OF VIRUS



The mechanism of viral entry is as follows. The S protein mediates the virus entry into the cell by binding its receptor, followed by fusion and endocytosis (1). So, the virus has spike protein that recognises human cell receptor ACE2. It is believed that the fusion occurs at a low pH between viral and host target membranes via S2 subunit. After the entry, the viral genome, a single stranded RNA, is launched into the cytoplasm and translated into two large polypeptides (pp1a and pp1ab), which are fragmented and transformed into mature functional proteins by the two viral proteases $3CL^{PRO}$ (3C-like protease or main protease) and PL^{PRO} (papain-like protease). Also, the RNA replication occurs producing multiple copies of the genome. This process is mediated by the viral replication complex, including the RNA-dependent RNA polymerase (RdRp), helicase, and other accessory (non-structural) proteins. Structural viral proteins such as membrane, spike and envelope proteins are synthesized in the cytoplasm and then placed in the endoplasmic reticulum - Golgi Body compartment. Hence, plenty of these building blocks are formed in a virus infected cell and spontaneously self-assemble to generate new viruses. Finally, these viruses are exported from the infected cell through a process called exocytosis (2) and infect other cells.

SARS-CoV-2 infection cycle displays different steps. Potential targets for some selected antiviral drugs to interfere in different steps of infection cycle are shown on the previous page. Use of ~~camo~~ camostat and mesylate to block virus/host cell interaction and inhibition of virus entry; use of hydroxychloroquinone lowers the pH that inhibits endosome maturation; use of Lopinavir-Ritonavir as protease inhibitors to inhibit viral polypeptide synthesis; Remdesiwir as nucleoside/nucleotide analogues to inhibit RNA polymerase intervening viral genome replication; Dexamethasone as an anti-inflammatory drug to control immune response.

SARS-CoV-2 has 16 highly conserved non-structural proteins (nsps) which present different functions. Some of these have very specific roles and these are the main protease (M^{pro}), the papain-like protease (PL^{pro}), the RNA dependent RNA polymerase (RdRp), and these nsps are druggable targets due to availability of the crystal structures along with their essential roles in viral infections.

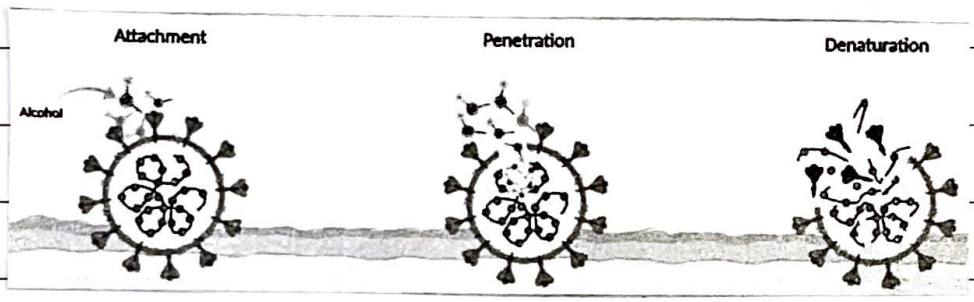
CHEMISTRY OF VIRULENCE

Cells, tissues and organs that express the ACE2 receptor and are infected by SARS-CoV-2 undergo the following. The S (spike) protein (with its S1 and S2 subunits) interact with ACE2 leading to conformational changes in the protein that facilitate the proteolytic cleavage of the S protein that further exposes the fusion peptide (FP). This S cleavage is catalysed by several host proteins and endosomal enzymes. All these proteolytic cleavages expose the fusion peptide (FP) of the S2 subunit of the virus, facilitating virus-cell membranes fusion and the entry of viral RNA + genome into the cell, starting the SARS-CoV-2 infection process.

Nano-based strategies to battle SARS-CoV-2 (COVID-19) must confront all symptoms of the disease, particularly to avoid severe outcomes, and to neutralise the infection of cells from different tissues and organs that could be targeted by the virus, through vaccine-elicited specific and optimal immune responses, mainly driven against the S viral immunogen.

VIRUCIDAL ACTION OF HAND SANITISERS

Several antimicrobial compounds have been used for hand disinfection - alcohols, chlorhexidine, chloroxylenol, hexachlorophene, benzalkonium chloride, cetrimide, triclosan and povidone-iodine. The alcohols - ethanol and isopropanol, are most commonly used. Their mode of action against enveloped viruses:



ANTIVIRAL MECHANISM OF ACTION OF ALCOHOL AGAINST ENVELOPED VIRUSES.

Lipid membrane dissolution and protein denaturation are key mechanisms of the antimicrobial action of ethanol, leading to the disruption of membrane and inhibition of metabolism. Alcohols are amphiphilic compounds, as they possess both hydrophylic and lipophilic (hydrophobic) properties that facilitate their entry through the viral envelope. The outermost membrane of SARS-CoV-2 comprises lipids bound together by an alkaline chain of hydrophobic fatty acids. Contact of the virus with an alcohol leads to alteration in its membrane fluidity. The presence of polar oxygen atoms weaken the lipophilic interactions between the non-polar residues, and increase the internal affinity of the membrane for water, thus destabilising and denaturing the protein structure.

ALCOHOL TYPE AND CONCENTRATION

Isopropanol is more lipophilic than ethanol, thus is less active against hydrophilic viruses such as polioviruses. Being a lipophilic enveloped virus, SARS-COV-2 exhibits a greater susceptibility to isopropanol over ethanol.

The optimum bactericidal concentrations of alcohols range from 60% to 90% v/v solutions (3) in water but are generally ineffective against most microorganisms below 50% v/v. A recent study has shown that >30% concentrations of ethanol or isopropanol were effective in inactivating SARS-CoV-2 within 30s.

WHO FORMULATIONS FOR HAND DISINFECTION

Formulation 1: Ethanol 80% v/v, glycerol 1.45% v/v, hydrogen peroxide (H_2O_2) 0.125% v/v

Formulation 2: Isopropanol alcohol 75% v/v, glycerol 1.45% v/v, hydrogen peroxide (H_2O_2) 0.125% v/v.

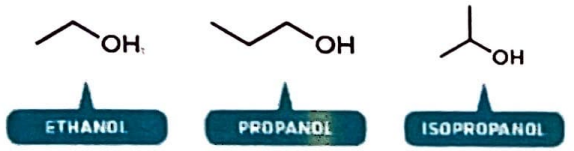
A revision increased the concentration of isopropanol to 91% v/v in Formulation 2.

pH REQUIREMENTS

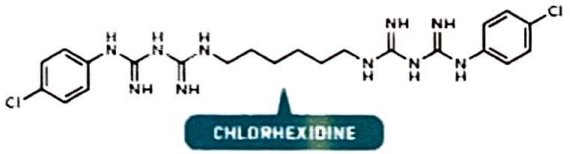
Corona viruses are reported to be more stable at a slightly acidic pH but mild alkaline (pH 8) conditions are sufficient to induce conformational changes in the spike proteins. Both high and low pH cause inactivation of SARS-CoV.

HOW HAND SANITISERS PROTECT AGAINST INFECTIONS

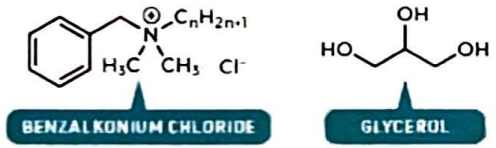
WHAT'S IN HAND SANITISERS?



Alcohol-based sanitisers contain 60-95% alcohol. Most contain either ethanol, n-propanol, isopropanol, or a combination of these.



Chlorhexidine and benzalkonium chloride are also found in some sanitisers. Both are also used in non-alcohol-based sanitisers.



Other ingredients include glycerol, which acts as a moisturiser to stop your skin drying out. Hydrogen peroxide is added to prevent bacterial contamination in the hand sanitiser.

HOW DO HAND SANITISERS WORK?

Alcohols in hand sanitisers alter (denature) the structure of proteins. They destroy the cell wall and membranes of bacteria cells, and the envelope of viruses (including coronavirus). They're less effective against non-enveloped viruses. Non-alcohol-based sanitisers also kill bacteria but are less effective against viruses.

HOW EFFECTIVE ARE THEY?

MINIMUM OF 60% ALCOHOL

Hand sanitisers with >60% alcohol are effective if applied generously. However, they don't kill all virus types and are less effective on dirty or greasy hands.

WASH HANDS FOR 20 SECONDS

Hand washing with soap for 20 seconds washes away bacteria and viruses, and also removes dirt and grease. Antibacterial soaps are no more effective.

CHEMISTRY OF SOAPS AND HANDWASHING

Hygiene measures such as handwashing are critical for disease prevention. Frequent handwashing may cause serious damage to the skin. Skin damage increases the risk of secondary infections by staphylococci and Gram-negative bacteria. Hence, optimal surfactants which cause minimal ~~Skin~~ damaged are important.

Fatty acid salts, surfactants generated from natural fats, have low cytotoxicity (4) and don't cause skin damage. Studied here are the interactions and molecular assembly in the mixtures of viruses with fatty acid salts to elucidate the mechanisms of virus inactivation by fatty acid salts.

Potassium tetradecanoate ($C_{14}K$) as a fatty acid salt and potassium oleate ($C_{18=1}K$) as a control of the fatty acid salt. The virus in which RNA was inactivated by UV radiation was used as virus particle (VP). The VP was dispersed in a phosphate buffer solution and a hemagglutinin vaccine was used. Since the attractive interaction of fatty acid salts with VP is related to effective inactivation of the virus, it is considered that the attractive interaction between fatty acids salts with hemagglutinin (HA) plays an important role in the effective inactivation of the virus.

It was found that potassium salts of fatty acids strongly bind to HA of influenza virus through exothermic interactions, such as electrostatic interactions. This attractive interaction between the fatty acid salt and HA results in rapid molecular assembly into an ordered lamellar structure and inhibition of HA function.

The mechanism of HA inhibition of fatty acid salt is considered to be universal for viruses covered with an envelope such as SARS-CoV-2. Because the natural soaps consisting of fatty acid salts have low cyto-toxicity and are not damaging to skin, handwashing with these products is an effective measure to prevent infectious diseases caused by enveloped viruses without adverse effects.

CHEMISTRY OF SURFACE DISINFECTION

BLEACH FOR SURFACE SANITIZATION

Fomite surfaces are generally sanitized by disinfectant spray, for instance, chlorine-based bleach, which is an aqueous solution of sodium hypochlorite (NaClO). The chlorine based bleach is commonly used for household disinfection and cleaning. NaClO is unstable in solution and relatively stable as dilute conditions that have solvated Na^+ and ClO^- ions and this stoichiometric solution is alkaline in nature - $pH \geq 11$. Because hypochlorous acid is a weak acid whereas NaOH is a strong base as given:

$$NaOCl + H_2O \rightleftharpoons HOCl + NaOH$$

The following species are formed in solutions:

$$HOCl\ (aq.) \rightleftharpoons H^+ + ClO^-$$

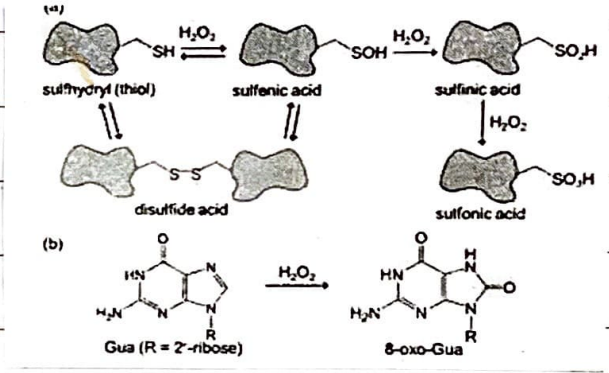
$$HOCl\ (aq.) + Cl^- + H^+ \rightleftharpoons Cl_2\ (aq.) + H_2O$$

Bleach oxidises and destroys virus proteins and genetic materials, as NaClO is unstable in solution and easily decomposes to Cl_2. The surfaces should be exposed to hypochlorite solution for at least 10 mins to kill the viruses. Hypochlorite can be used only on hard fomite surfaces unless it's diluted to 0.05%. High concentration of Cl_2 in commercial bleach can cause corrosion of metal, alloy, many thermoplastics, and irritation of skin with potential side-effects.

HYDROGEN PEROXIDE FOR SURFACE SANITIZATION

H_2O_2 solution can only be applied on hard / fomite surfaces, not on our hands and the minimum concentration is 0.5%. It oxidises and destroys virus proteins and genetic materials and it should be left on surfaces for at least 10 mins for killing viruses. H_2O_2 oxidises the proteins and RNA of the viruses. The protein's residue contains thiol group and it is oxidised to disulphide and other analogues like sulfenic acid, sulfinic acid and finally sulfonic acid by H_2O_2.

EQUATIONS FOR H_2O_2 SURFACE SANITIZATION



CHEMISTRY OF DIAGNOSIS

The tests currently being used to identify coronavirus infection are known as PCR (polymerase chain reaction) tests. These tests allow copying of a small amount of DNA millions of times over so there is enough for detection and confirmation of infection. Some other tests being used include:

(5)

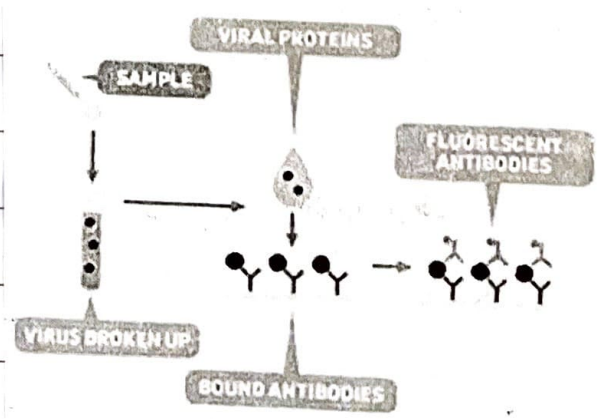
ANTIBODY TESTS

They identify if a person has antibodies to the virus. If they do, they had an infection in the past. Many types of antibody tests are available. They all aim to detect antibodies in a person's blood, serum, or plasma sample. Most tests work by mixing a person's sample with viral proteins or protein fragments. Any antibodies the person generated will bind to these. Then a reporter molecule, such as a fluorescent antibody, is added to detect past infection.

(6)

ANTIGEN TESTS

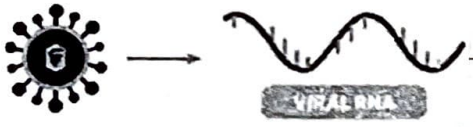
Antigen tests look for fragments of viral proteins to confirm that a person is currently infected with the virus. They can be carried out in a variety of ways. Most use a sample collected on a swab, though



some use blood samples. Virus in a collected sample is chemically broken up in a solution and added to a slide coated in antibodies. The antibodies bind to the viral proteins. Then, fluorescent antibodies are added, which attach to confirm a positive result.

NUCLEIC ACID TESTS

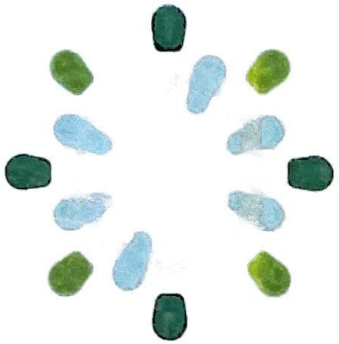
Nucleic acid tests detect a virus's genetic material to confirm that a person is currently infected with the virus.



Virus RNA is extracted from a nose or throat swab. An enzyme called a reverse transcriptase converts the RNA to DNA.

In some tests, polymerase chain reaction makes millions of copies of the transcribed DNA. Short, virus-specific oligonucleotide probes with a fluorophore on one end bind to the copies. An enzyme cleaves the probe, causing fluorence and confirming infection.

ANTIBODY TESTS PART 1: WHAT THE TESTS TELL US



WHAT ARE ANTIBODIES?

Your body makes antibodies when it detects an infectious agent (an antigen). Antibodies neutralise and destroy antigens.

Variable region of antibody
Different for different diseases

Constant region of antibody
Identical in antibodies of the same type

Once we've recovered from an infection, our immune cells "remember" the antigen. If we are reinfected, antibodies are rapidly made to remove it. This is immunity; it's life-long for some diseases and fades over time for others.

WHAT ANTIBODY TESTS TELL US

Antibody tests usually test for the presence of two different types of antibody: IgM and IgG. IgG is the most common antibody produced in the body in response to an infection.

IgM antibodies	IgG antibodies
Production starts 5–10 days after infection	Production starts 10–14 days after infection
Production peaks around 21 days after infection	Production peaks 4–8 weeks after infection
Remain detectable 2–4 months after infection	Remain detectable for months or years after infection

Antibody tests can tell us if someone has had an infection in the past.

ANTIBODY TEST RESULTS

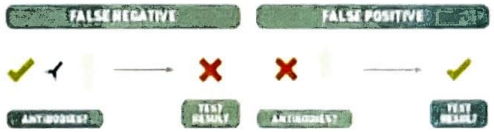
IgM	IgG	Result
✗	✗	No infection*
✓	✗	Early-stage infection
✓	✓	Active/recent infection
✗	✓	Past infection

*Antibodies don't appear until someone has had an infection for several days, so this doesn't guarantee they're not infected.

Having antibodies against an antigen isn't a guarantee of immunity. Levels of antibodies and their effectiveness are also important.

ANTIBODY TEST ACCURACY

The accuracy of antibody tests is determined by their sensitivity and their specificity. These measures tell us how often a test produces false negative and false positive results.



A false negative is when the test returns a negative result when someone has antibodies against an antigen. A false positive is when the test returns a positive result for someone who doesn't have antibodies against the antigen.

SENSITIVITY

Sensitivity measures the correct production of positive results. The higher the sensitivity, the fewer false negative results are produced.

Test sensitivity = 90%

SPECIFICITY

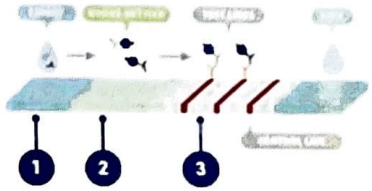
Specificity measures the correct production of negative results. The higher the specificity, the fewer false positive results are produced.

Test specificity = 90%

ANTIBODY TESTS PART 2: HOW DO THE TESTS WORK?

RAPID DIAGNOSTIC TESTS

These tests are similar to pregnancy tests. They are small, portable, and give quick results.



1. The patient sample is added here. The sample and any antibodies it contains then flows down the strip.
2. This part of the test strip contains the antigen attached to gold nanoparticles. If there are antibodies in the patient sample for the antigen they bind to it, carrying the antigen (and the gold particles) with them.
3. At the test lines, antibodies from the sample are captured. The gold nanoparticles they carried with them make the test line turn red to indicate a positive test. The control line shows the test has worked correctly.

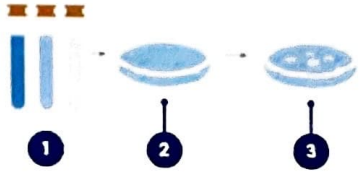
✓ The test usually takes 10–30 minutes.

WHAT CAN THIS TEST TELL US?

- ✓ Are antibodies present in the sample?
- ✗ The level of antibodies in the sample
- ✗ How effective are the antibodies?

NEUTRALISATION ASSAY TEST

This test is lab-based and takes several days. It can tell us how effectively patient antibodies can neutralise a virus.



1. Serial dilutions of the patient sample are mixed with a suspension of the virus (the concentration of which remains constant).
2. The combination of patient samples and virus suspensions are incubated then added to host cells in a petri dish. The dishes are covered in agar and incubated.
3. A plaque forms on the dish contents over several days. Antibodies to the virus in the patient sample reduce plaque formation. Results at different dilutions help us know how effectively the patient antibodies block the replication of the virus.

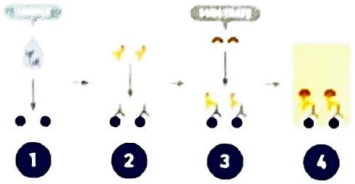
✓ The test usually takes 3–5 days.

WHAT CAN THIS TEST TELL US?

- ✓ Are antibodies present in the sample?
- ✗ The level of antibodies in the sample
- ✓ How effective are the antibodies?

ELISA

Enzyme-linked immunoabsorbent assay tests (ELISA) are lab-based and take a few hours. A common example is shown below.



1. The patient sample is added to a microplate well coated with deactivated antigen or a protein from the antigen, then incubated.
2. If the patient sample has antibodies to the antigen, they bind to the antigen or protein. Enzyme-labelled antibodies are then added which bind to the patient antibodies.
3. The enzyme substrate is added.
4. The substrate changes colour when it binds to the enzyme. The intensity of the colour links to the level of antibodies in the sample.

✓ The test usually takes 2–5 hours.

WHAT CAN THIS TEST TELL US?

- ✓ Are antibodies present in the sample?
- ✓ The level of antibodies in the sample
- ✗ How effective are the antibodies?

OTHER IMMUNOASSAYS

A number of other tests work on a similar basis to ELISA but have notable differences.

CHEMILUMINESCENT IMMUNOASSAY (CLIA)

Similar to ELISA, but the substrate added causes a light-producing chemical reaction. The amount of light produced links to the sample antibody levels.

✓ The test usually takes 1–2 hours to run.

ELECTROCHEMILUMINESCENCE IMMUNOASSAY

Uses electrochemiluminescent labels, which produce light when an electric current is applied. The amount of light produced links to the sample antibody levels.

✓ The test usually takes under an hour.

OTHER TYPES

Other types of immunoassay include fluorescence and microsphere immunoassays.

WHAT CAN THESE TESTS TELL US?

- ✓ Are antibodies present in the sample?
- ✓ The level of antibodies in the sample
- ✗ How effective are the antibodies?

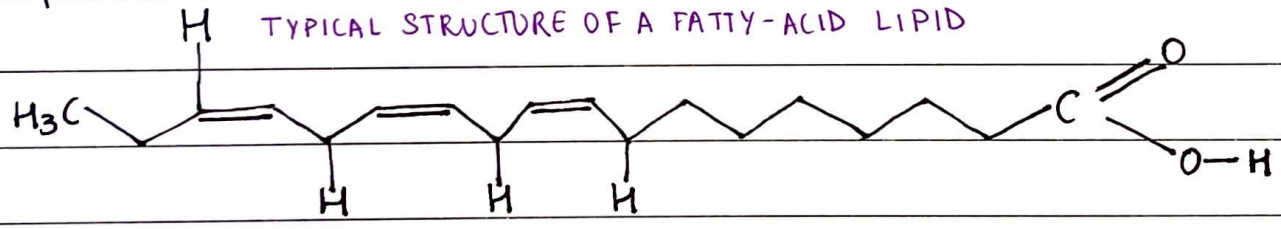
INACTIVATION OF ENVELOPED VIRAL AEROSOLS

The analysis of the inactivation of enveloped viral aerosols will be done in terms of oxidation of the lipid bilayer of the viral envelope through a free radical chain reaction. Transmission of SARS-CoV-2 within an aerosol droplet is plausible since the virus can remain viable and infectious for significant periods.

VIRUS INACTIVATION

In some viruses, like coronaviruses, the capsid of the virion with its enclosed nucleic acid is surrounded by a lipoprotein envelope. The bilayer envelope of those viruses is derived from ~~proteins of~~ portions of host cell membranes and includes anionic lipids. The role of the lipids in virus replication is inevitably intricate. The envelope has many functions in viral infections including virus attachment to cells, entry into cells, the release of the capsid contents into the cells and the packaging of newly formed viral particles.

TYPICAL STRUCTURE OF A FATTY-ACID LIPID



The most common mechanism of the degradation of lipids is environmental oxidation through the effects of light, humidity, and atmospheric oxygen, all of which can accelerate the breakdown of the lipid molecular chain, and that oxidation occurs wherever unsaturated fatty-acid lipids are found. The process by which lipid oxidation occurs is a free radical chain reaction with the stages of initiation, propagation and termination leading to a series of complex chemical changes.

In the presence of an environmental indicator like light, the viral envelope lipid loses a hydrogen atom and produces free radicals.

We represent a single viral lipid as VL_1H and initiation, the formation of an ab initio viral lipid free radical ($VL_1^{\cdot}$), can be represented by:

$$VL_1H \xrightarrow{\text{removal of H}} VL_1^{\cdot}$$

The viral lipid radical reacts with aerial O_2 to form a peroxyl radical, $VL_1OO^{\cdot}$,

$$VL_1^{\cdot} + O_2 \longrightarrow VL_1OO^{\cdot}$$

which acts as the chain carrier for propagating the reaction by attacking an adjacent viral lipid, VL_2H, to form another viral lipid radical ($VL_2^{\cdot}$) and hyperperoxide (VL_1OOH),

$$VL_1OO^{\cdot} + VL_2H \longrightarrow VL_1OOH + VL_2^{\cdot}$$

followed by a series of reactions,

$$VL_2^{\cdot} + O_2 \longrightarrow VL_2OO^{\cdot}$$

$$VL_2OO^{\cdot} + VL_3H \longrightarrow VL_2OOH + VL_3^{\cdot}$$

and so on. The free radical chain is thus established

From a single initiation, this reaction can be repeated many times during propagation until termination where no hydrogen source is available or radical scavenging becomes excessive.

Thus, viral lipid oxidation is self-propagating.

Since the proteins on the surface of the envelope serve to identify and bind to receptor sites on the host's membrane when the viral envelope fuses with it, allowing the capsid and viral genome to enter and infect the host, it would not be suprising that extensive oxidative rupturing of the lipid structure would disturb infection transmission.

KINETICS OF VIRUS INACTIVATION

Although there is a series of equations (previous page), the overall oxidation can be simply written as:

$$VLH + O_2 \longrightarrow VLOOH$$

to form a hyperperoxide, VLOOH.

The hyperperoxides are the predominant products and are relatively stable, so they build up with time. Hence their formation can be treated as coming from bimolecular oxidation and we can use;

$$VLH + O_2 \longrightarrow VLOOH$$

as the overarching process.

A viral hyperperoxide will have a different structure from the initial viral lipid, VLH, and would be expected to induce a different viral activity and to impede infection transmission; in other words, viral deactivation will occur.

The rate of viral deactivation is given by:

$$\frac{d[VLH]}{dt} = -k_2 [VLH] \times [O_2]$$

(k_2: constant of proportionality)

which gives the rate of disappearance of the active viral lipid VLH, usually with units mol/l/s

Oxygen will always dwo be the dominant reactant because the dissolved O_2 will never be depleted. Thus $[O_2]$ is effectively constant:

$$\frac{d[VLH]}{dt} = k'[VLH]$$

(k': pseudo-first order rate constant)

Integration of this shows exponential decay of virus concentration with time:

$$[VLH] = [VLH]_0^{(-k't)}$$

To halve the initial conc. $[VLH]_0$ ($t = t_{1/2}$), for SARS-COV-2 is 1.1hr and for SARS-COV-1 is 1.2 hr. The relationship between a pseudo-first order rate constant and half life is given by:

$$k' = \frac{\ln 2}{(t_{1/2})}$$

So the two rate constants are 1.75×10^{-4}/s and 1.60×10^{-4}/s. The kinetics of the inactivation of the two viruses is very similar. Published comparisons of enveloped viruses are related to medical considerations like transmissibility, hospitalizations, mortality rates, pathogenisis, and epidemiology. The similarities between the kinetic characteristics with comparable generic behaviour of lipids, irrespective of the environment; shows the usefulness of considering the chemistry of inactivation.

CHEMICAL STRUCTURES OF REPURPOSED DRUGS FOR TREATING COVID-19

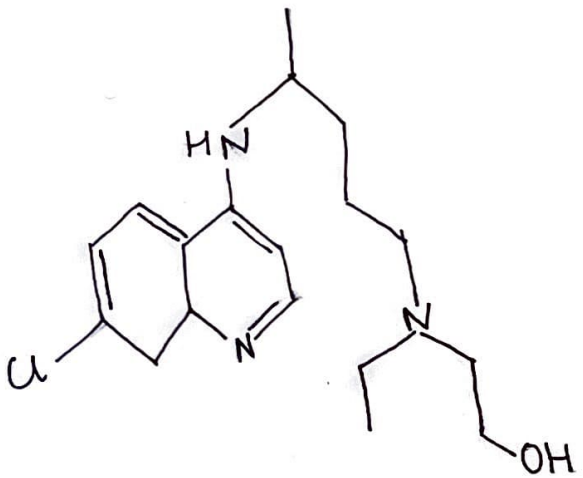
HYDROXYCHLOROQUINE (HCQ)

HCQ is a well-known drug for treating malaria and this was being used in some countries during the crisis of ~~lack~~ lack of drugs for COVID-19 patients. For SARS-CoV-2, HCQ, being a weak organic base, passively diffuses via cell membranes, gets protonated and increases the pH in endosomes, inhibiting virus particles from fusion after entering the cell. Recent studies have shown that HCQ was not active enough against SARS-CoV-2 even though it decreased death rates in HCQ-treated patients. By the use of molecular dynamics approaches with atomistic insights, it has been demonstrated that HCQ may slightly inhibit functional proteins which are required for SARS-CoV-2 replication.

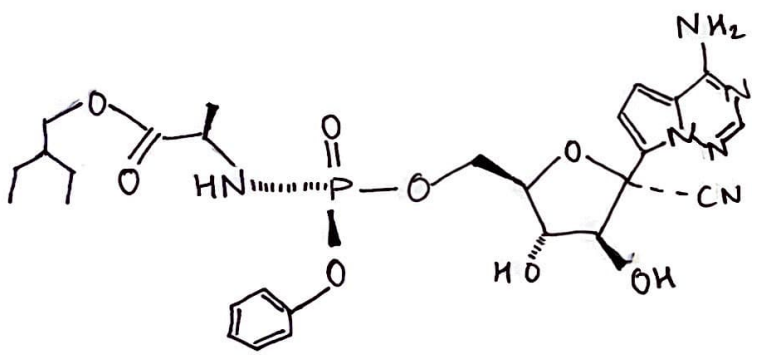
REMDESIVIR

Remdesivir was previously tested for the treatment of ebola. Among all the tested candidates, Remdesivir was found to be the most promising drug for COVID-19 because of its wide range of in vitro activity against coronaviruses, including SARS-CoV-2. Remdesivir is a monophosphate nucleotide analogue prodrug, a compound that, after administering, is metabolized and converted to an active drug. In case of Remdesivir, it is transformed to a pharmacologically active derivative of ATP in the cell and interferes in viral RNA replication process and thus reduces the time of recovery from COVID-19 by several days. It's not enough to be called a 'cure', but it's likely to relieve some pressure.

HYDROXYCHLOROQUINE (HCQ)



REMDESIVIR



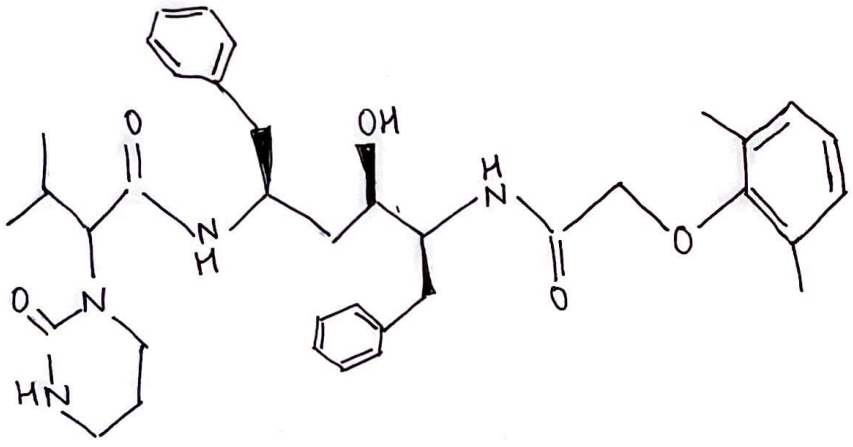
LOPINAVIR / RITONAVIR

A mixture of 2 HIV-1 protease inhibitors, namely Lopinavir and Ritonavir, was known to be useful against SARS-CoV-1. When Lopinavir is administered alone, it has a very low human bioavailability of around 25% mainly due to its extensive metabolism by P450 CYP3 A4 enzymes. It is mostly co-administered with Ritonavir, which reduces drug metabolism and significantly improves the bioavailability of Lopinavir. The chemical structures of these drugs are similar to small peptides which include highly modified synthetic amino acids. Previously Lopinavir has been seen to inhibit the replication of MERS-CoV and SARS-CoV-1 to some extent.

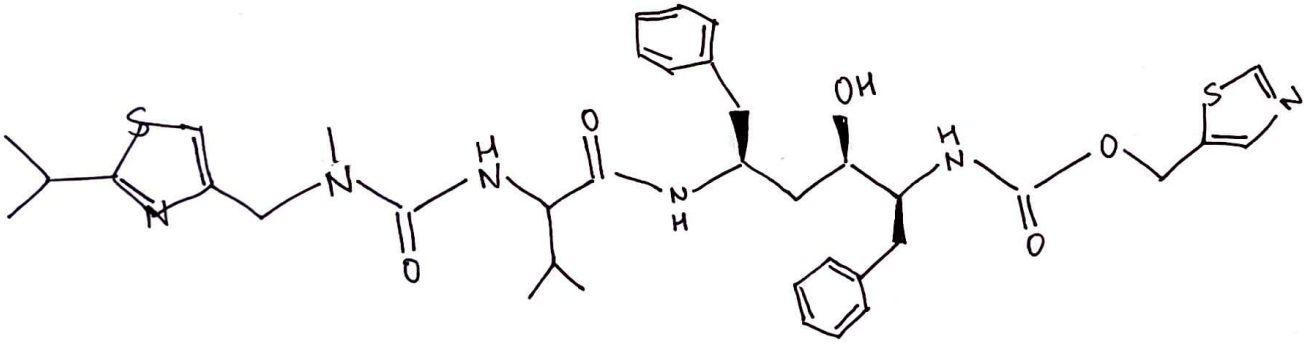
After entering the host cells, the SARS-CoV-2 virus replicate forming strands that contain multiple copies of RNA and the enzyme $3CL^{pro}$ (3-chymotrypsin-like protease) plays a key role in processing viral RNA. Being a protease inhibitor, Lopariwir may act as an inhibitor for $3CL^{pro}$ and hence it can interrupt the viral replication process.

Both drugs showed significant interaction with the residues at the actic site of SARS-CoV-2 $3CL^{pro}$. This study shows how repurposed anti-HIV drugs can be exploited to fight COVID-19 and how computational chemistry at the atomic level is imperative for the discovery of more specific drugs in fighting coronavirus.

LOPANAVIR



RITONAVIR

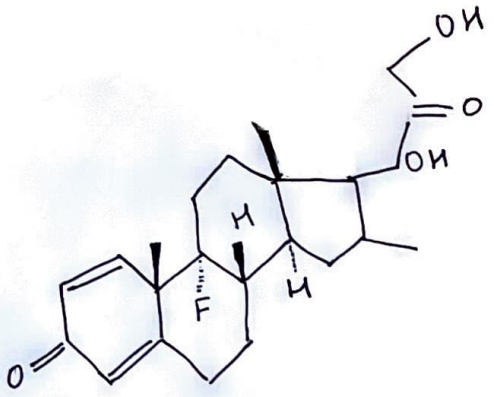


DEXAMETHASONE

Dexamethasone has been found to have benefits for seriously ill COVID-19 patients on ventilators and the treatment was revealed to reduce mortality by approximately 1/3rd. Dexamethasone is a well known corticosteroid medication and has long been used in many conditions for its anti-inflammatory effect.

The sickest COVID-19 patients suffer a hyperinflammatory state, a cytokine storm, (7) where immune suppression could bring them temporary relief. The $3CL^{pro}$ on SARS-CoV-2 inhibits HDAC2 transport into the nucleus, and hence weakens the way in which it mediates inflammation and cytokine responses. Therefore, it is assumed that Dexamethasone can activate histone deacetylase and directly inactivate SARS-CoV-2 infection. Dexamethasone is a derivative of cortisol (hydrocortisone) and chemically described as 1-dehydro-9α-fluoro-16α methylhydrocortisone or as 9α-fluoro-11β, 17α, 21-trihydroxy-16α-methylpregna-1, 4-diene-3, 20 dione.

DEXAMETHASONE



CONCLUSION

There is an immeasurable synergy between chemistry and biology to fight COVID-19. Several areas of chemistry - supramolecular self assembled structure, surfactant bilayers, analysing structures of proteins, molecular ~~leg~~ recognition in the context of structure and host binding of SARS-COV-2 - have key roles in finding solutions to the pandemic.

In conclusion, the whole chemical science community has been contributing to this fight. This was an incredibly informative topic to research and I have come away with a great deal more knowledge that I could have previously imagined.

GLOSSARY

(1) ENDOCYTOSIS: cellular process by which substances are brought into the cell.

(2) EXOCYTOSIS: cellular process by which substances are removed from the cell.

(3) V/V% : percent by volume of a solution

(4) CYTOTOXCITY: A substance that kills cells

(5) ANTIBODY: Protein produced by immune system in response to a foreign substance.

(6) ANTIGEN: A substance that causes your body to produce antibodies against it.

(7) CYTOKINE STORM: Release of many life threatening glycoproteins

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