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A BRIEF REVIEW ON IN SILICO COMPARISON OF PHARMACOKINETIC PROFILES AND ADMET CONSTRAINTS: EVALUATING PHYTOCHEMICALS VERSUS SYNTHETIC ANALOGUES AS SARS-COV-2 INHIBITORS

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ABSTRACT

The quick identification of antiviral medications that target SARS-CoV-2 was made necessary by the COVID-19 pandemic. The success of possible drug candidates is largely dependent on their Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties. Predicting ADMET qualities early on is crucial to preventing late-stage attrition because these characteristics are frequently rate-limiting in the drug development process. This paper offers a thorough in silico comparison of several phytochemicals with well-known synthetic analogues, such as Remdesivir, Nelfinavir, and Favipiravir. Phytochemicals were assessed against five crucial therapeutic targets using virtual screening via molecular docking and simulations: 3 Clpro (Mpro), RdRp, and ACE2. Despite sporadic issues with bioavailability and Lipinski's Rule breaches, our comparative research shows that phytochemicals typically display superior safety profiles and reduced toxicity, whereas synthetic medicines commonly exhibit high potency. The results imply that these identified phytochemicals' fundamental structures can be used as models for lead optimization.

KEYWORDS: SARS-CoV-2, ADMET, Phytochemicals, Molecular Docking, 3CLpro, RdRp, In Silico, Drug Discovery, Lead Optimization, Bioavailability.

INTRODUCTION

The highly contagious positive-sense single-stranded RNA virus is known as SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2). As of early 2026,[2] it is still spreading around the world, with public health surveillance concentrating on new lineages like as BA32 and the NB.1.8.1 (Nimbus) group, which show considerable potential for immunological escape but have not yet produced the fast surges associated with early Omicron strains.

Transmission and pathogenesis

Cellular Entry: Respiratory epithelial cells are the main cells that the virus infects. The host enzyme TMPRSS2 primers the Spike protein, which enables the virus to enter through endocytosis or merge with the cell membrane.[12]

Organ Involvement: Although largely a respiratory pathogen, the gastrointestinal tract, liver, and pancreas are prominent extrapulmonary sites for infection due to strong ACE2 expression in these organs.[12]

Transmission: Aerosols and respiratory droplets are the primary means of transmission. Although the clinical importance of fecal-oral transmission is still being studied, The four main structural proteins encoded by the SARS-CoV-2 genome are Spike (S), Envelope (E), Membrane (M), and Nucleocapsid (N). Non-structural proteins (nsps), such as the Main Protease (Mpro) and Papain-like Protease (PLpro), are essential enzymatic targets for interfering with the viral life cycle, whereas structural proteins make up the actual viral particle.[12]

Spike (S) Protein: The "Gatekeeper" By attaching to the ACE2 receptor, the trimeric class I fusion glycoprotein known as the Spike protein facilitates viral entrance into host cells.

Vaccines: To generate immunological responses, the majority employ either RBD or the full-length S protein. In Silico Focus: In order to prevent this binding, phytochemicals (such as kaempferol) are frequently docked to the RBD.[7]

Main Protease (3CLpro/Mpro): Because of its high conservation and lack of a human homolog, which lowers the possibility of off-target toxicity, Mpro (Nsp5) is perhaps the most "druggable" target. Nirmatrelvir (Paxlovid), a covalent inhibitor that attaches to the Cys145 residue, is one of the approved inhibitors.[3,7]

Rather than being ineffective, inadequate ADMET characteristics have historically caused 40–60% of medication candidates to fail clinical trials.

Researchers can do the following with in silico (computational) studies:

- Filter Candidates Early: Use Veber's criteria or Lipinski's "Rule of Five" to get rid of "lead-like" compounds that the human gut won't absorb.[9]
- Predict Toxicity: Prior to any animal testing, identify possible hepatotoxicity (liver) or hERG inhibition.[9]
- Optimize Lead Compounds: In silico modeling can recommend structural changes (synthetic analogs) to enhance a phytochemical's profile if it has strong binding but poor solubility Examining these two classes' performance under the "ADMET microscope" is useful, particularly for SARS-CoV-2 targets like Mpro (3CLpro), PLpro, and RdRp.[9,7]

1. Comparative Profiling: Evaluate high-performing phytochemicals' in silico ADMET scores in comparison to FDA-approved synthetic antivirals.

2. Dispelling the "Natural" Myth: Make use of evidence to refute the notion that "natural" equates to "better PK." The "D" (Distribution) and "M" (Metabolism) phases are when many phytochemicals falter.
3. The Hybrid Solution: Talk about how semi-synthetics, or synthetic analogs of phytochemicals, can close the gap by preserving the natural binding scaffold while correcting the pharmacokinetic "flaws."

3. METHODOLOGY

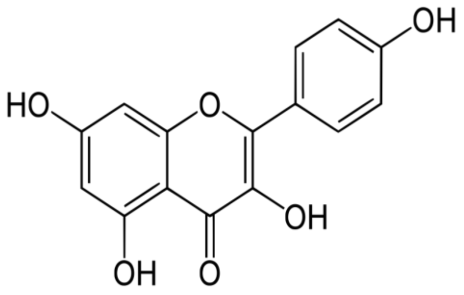
ADMET analysis: The SWISSADME server was used to conduct studies on absorption, digestion, metabolism, excretion, and toxicity. Lipophilicity, solubility, and drug likeness score were obtained by uploading the drug's structure and phytochemicals.

Phytochemicals' Similarity to Drugs: Lipinski's value was used to screen the phytochemicals against the medications.[9]

A set of criteria known as Lipinski's Rule of Five (RO5) enables the early detection of drug-like characteristics in phytochemicals and pharmaceuticals.

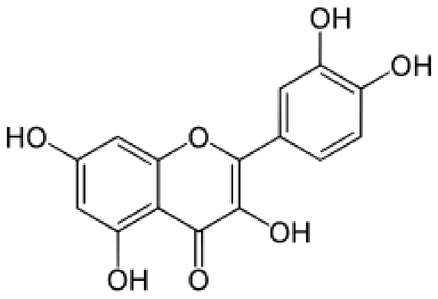
Phytochemicals as SARS-CoV-2 Inhibitors

Main Protease Inhibition: This is the most widely cited mechanism. Kaempferol binds to the active site of the 3-chymotrypsin -like protease ($3CL^{pro}$), an enzyme essential for processing viral polyproteins into functional units.[3]



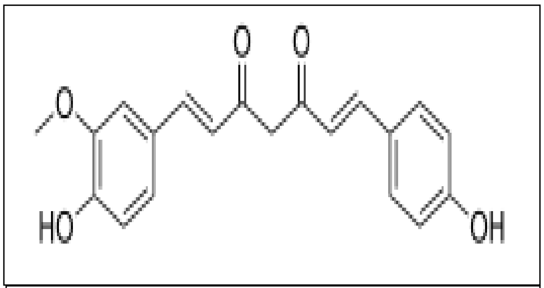
Kaempferol

Entry Blocking: It can bind to the **Spike (S) protein** of SARS-CoV-2, potentially preventing it from attaching to the **ACE2 receptor** on human cells.[14]

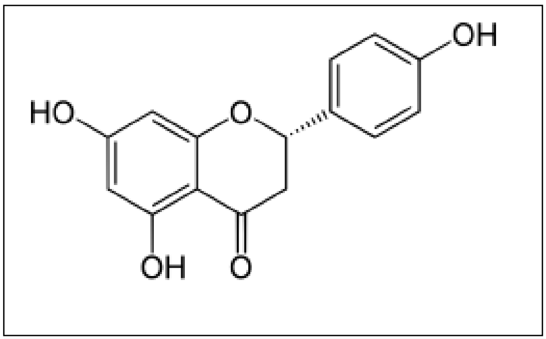


Quercetin

3CLpro (Main Protease) Inhibition: DMC acts as a potent inhibitor of the 3-chymotrypsin-like protease (3CLpro), the primary enzyme the virus uses to cleave its long polyproteins into functional units.[3]

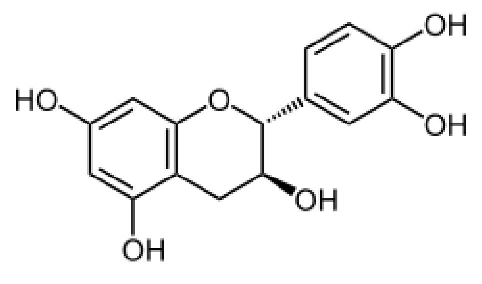


Demethoxycurcumin



Naringenin

Spike Protein Binding: *In silico* (computer modeling) studies indicate that Naringenin can directly bind to the **Receptor Binding Domain (RBD)** of the Spike protein, physically interfering with its ability to latch onto host receptors.[18]

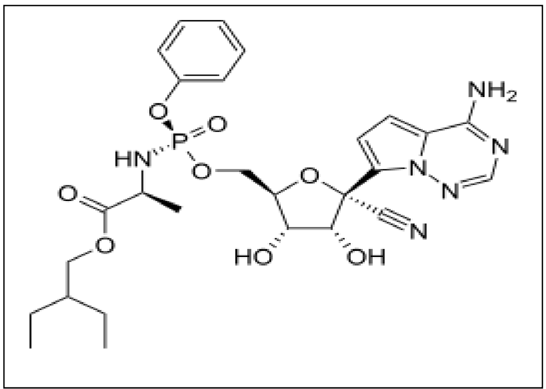


Catechin

Dual-Site Binding: EGCG has a high affinity for both the **SARS-CoV-2 Spike (S) protein** and the human **ACE2 receptor**. By binding to these sites, it acts like "molecular glue," preventing the virus from latching onto the lung cell.[3,23]

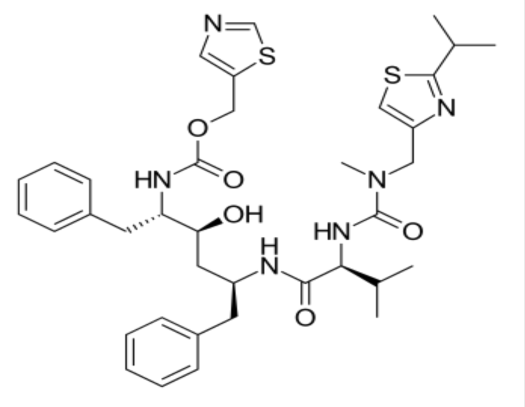
Synthetic Analogs as SARS-CoV-2 Inhibitors

Sabotaging the RNA Polymerase (RdRp) The "engine" of the SARS-CoV-2 virus is an enzyme called **RNA-dependent RNA polymerase (RdRp)**. This enzyme reads the original viral RNA and pulls in building blocks (nucleotides) to make new copies.[14]



Remdesivir

While Ritonavir is a protease inhibitor, it is **not active** against the SARS-CoV-2 Main Protease. Its structural design fits the HIV protease "lock," but it does not effectively fit the SARS-CoV-2 "lock." Therefore,; its value is almost entirely in its role as a metabolic "bodyguard."

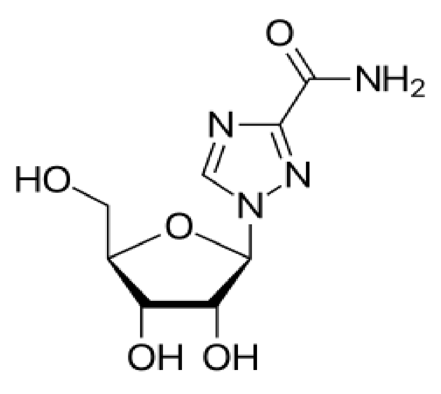


Ritonavir

Inhibition of RNA Capping

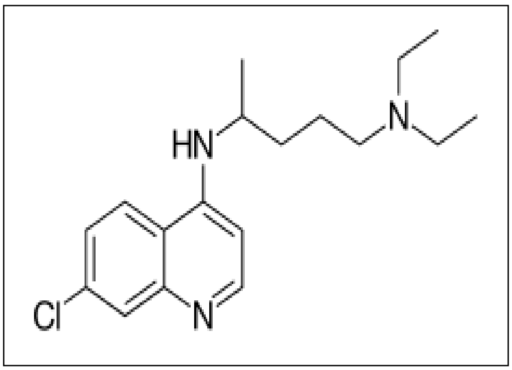
Viruses use a "cap" on the end of their mRNA to disguise it, making it look like human mRNA so the cell will translate it into viral proteins.[4]

Ribavirin interferes with the enzymes responsible for creating this **5' RNA cap**.



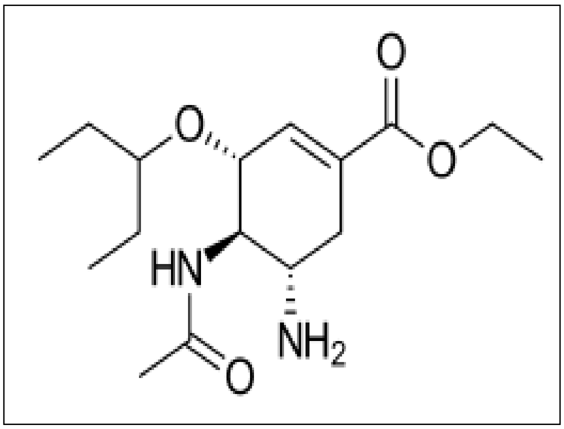
Ribavirin

ACE2 Receptor Disturbance: It can impair the glycosylation of the **ACE2 receptor**. If the receptor isn't "decorated" correctly with these sugars, the SARS-CoV-2 Spike protein cannot bind to it as effectively, reducing the initial infection rate of the cell.[14]



Chloroquine

Oseltamivir is a **Neuraminidase Inhibitor**. It blocks this "scissors" enzyme, effectively trapping the new viral particles inside the host cell so they cannot spread to neighboring cells.[21]



Oseltamivir

4. PARAMETERS EVALUATED

- Absorption: GI absorption, P-gp substrate, Caco-2 permeability
- Distribution: BBB permeability, VDss, Plasma protein binding
- Metabolism: CYP450 inhibition/induction
- Excretion: Total clearance, Renal OCT2 substrate
- Toxicity: Hepatotoxicity, AMES mutagenicity, hERG inhibition, LD50
- Drug-likeness: Lipinski's Rule of 5, Veber's rule, Bioavailability score

Phytochemical Profile

Compound	Absorption & Distribution	Metabolism	Excretion & Stability	Toxicity Profile
Kaempferol	High GI absorption; undergoes extensive first-pass metabolism.	Primarily metabolized in the liver via glucuronidation.	N/A	Generally non-toxic; high safety demonstrated in mouse models.

Quercetin	Obeys Lipinski's rules; poor water solubility.	N/A	Rapidly eliminated; stable when stored at $4^\circ\ {C}$ in solution.	Low toxicity; potential multi-target antidiabetic agent.
Naringenin	Extremely lipophilic; high distribution in organs (e.g., stomach).	Transformed by intestinal microflora into phenolic acids.	N/A	Practically non-toxic; NOAEL > 1250 mg/kg/day in rats.
Catechin	Rapidly absorbed.	N/A	Quickly cleared from plasma; excreted via renal and biliary pathways.	High safety profile; common dietary source.
Demethoxycurcumin	Moderate absorption; limited bioavailability.	Metabolized into glucuronide and sulfate conjugates.	Higher stability than curcumin.	N/A

Synthetic Drug Profile

These compounds are designed for high potency but often carry "black box" warnings or significant side effects that require clinical monitoring.[16,17]

Compound	Absorption & Distribution	Metabolism	Excretion & Stability	Toxicity Profile
Remdesivir	Administered IV; widely distributed to the lungs.	Pro-drug; converted to active nucleoside triphosphate.	N/A	GI symptoms, nausea, and elevated liver enzymes (transaminases).
Ribavirin	Good oral bioavailability; limited by physicochemical space.	N/A	Long half-life; accumulates in RBCs.	Hemolyticanemia and potential teratogenic effects.
Ritonavir	High oral absorption; potent CYP3A4 inhibitor.	Extensively metabolized in the liver.	Excreted mainly in faeces.	GI distress, perioral paresthesia, and major drug-drug interactions.
Chloroquine	Rapid and complete oral absorption; accumulates in lungs/liver.	N/A	Very slow excretion; remains in tissues for weeks.	QT prolongation (cardiac toxicity) and retinopathy.
Oseltamivir	Well-absorbed orally as a **pro**-drug (phosphate).	Converted to active carboxylate by hepatic esterases.	N/A	Nausea, vomiting, and rare neuropsychiatric events.

5. CONCLUSION

In silico analysis reveals that while synthetic analogues provide high-affinity binding to SARS-CoV-2 targets, The natural compounds serve as excellent leads for safe, long-term therapeutic use or dietary supplements due to their **low toxicity**.[31] However, the synthetic drugs remain the primary choice for acute viral infections because of their **targeted distribution** and optimized pharmacokinetics, despite their higher risk for adverse side effects and complex drug-drug interactions.[37]

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