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# Predicting global diet-disease relationships at the atomic level: a COVID-19 case study

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Over the past few months, numerous studies harnessed *in silico* methods such as molecular docking to evaluate food compounds for inhibitory activity against coronavirus infection and replication. These studies capitalize on the efficiency of computational methods to quickly guide subsequent research and examine diet-disease relationships, and their sudden widespread utility may signal new opportunities for future antiviral and bioactive food research. Using Coronavirus Disease 2019 (COVID-19) research as a case study, we herein provide an overview of findings from studies using molecular docking to study food compounds as potential inhibitors of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), explore considerations for the critical interpretation of study findings, and discuss how these studies help shape larger conversations of diet and disease.

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the potential biological importance of antiviral and other bioactive food compounds [2–4]. Indeed, food-derived polyphenols have demonstrated antagonistic properties against SARS-CoV, which was the culprit behind the 2003 SARS outbreak, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and other viruses [5–7].

While *in vitro* approaches have been and continue to be widely used to assess antiviral activity, the urgency and severity of the pandemic has prompted many studies to adopt *in silico* methods, which can predict molecular interactions much faster than *in vitro* approaches and with atomic-level detail. In particular, molecular docking has been used in numerous studies, oftentimes as a sole method, to screen food compounds for SARS-CoV-2 inhibitory activity. Although this method has been increasingly used in contemporary food science, it is predominantly used to evaluate molecular interactions during nutrient metabolism, and between bioactive peptides or functional, taste-inducing, or harmful compounds and their respective targets [8–10]. The vast majority of these studies employ molecular docking after *in vitro*, or even *in silico* [11], testing to assess the mechanisms underpinning observed results. Against a new target and its alarming threat on global health, however, the sole application of computational methods allowed for screening studies to be rapidly conducted and communicated. These studies capitalize on not only the efficiency of computational methods, but also the expanding databases of food-sourced compounds, decades of research on antiviral food compounds, and timely discoveries of SARS-CoV-2 from other fields including structural biology and pharmaceutical science. This recent surge of research thus presents a unique opportunity to assess COVID-19 as a case study for how molecular docking can be used in food research to understand diet-disease relationships.

## Accelerated food research in the pandemic world

The Coronavirus Disease 2019 (COVID-19) pandemic has led to a rapid increase of research on antiviral food-derived compounds, specifically those targeting Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Food compounds with biological activities in addition to their nutritional properties are generally considered safer for consumption than synthetic pharmaceutical drugs and have been receiving renewed interest in recent years as templates for drug design in light of genomic and technological advances [1]. Emerging evidence for the apparent protective effects of certain dietary practices and nutritional status on COVID-19 susceptibility and recovery further highlight

## Molecular docking for drug discovery

Molecular docking is a computational technique commonly used in pharmaceutical science to predict the fit of a compound to a target substrate, which is oftentimes a protein of clinical or functional importance. The determination of fit varies depending on the algorithms used and may take into account molecular spatial orientation, statistical models, and physicochemical interactions [12]. Using the structural information of both target and ligands, sampling algorithms first generate multiple conformations of each ligand associating with the target and scoring functions subsequently assign numeric scores to

each conformation and rank the overall scores [13]. The highest scored ligands are most likely to form stable complexes with the target, and therefore have highest potential to disrupt the function and activity of the protein target. Atomic-level interactions between each ligand-substrate pair can also be inferred from the docking results.

The efficiency and growing accuracy of molecular docking at evaluating large catalogs of compounds — exceeding 1 million in some cases [14] — for specific targets has increased the use of this technique in computer-aided pharmaceutical drug design workflows over the past few decades. Studies utilizing this method have played critical roles in the development of currently available drugs for the treatment of Human Immunodeficiency Virus (HIV) and influenza, and have contributed in the search for potential treatments of cancer, malaria, and other diseases [15]. Beyond screening and optimizing ligand potency for subsequent validation, this method has increasing applications in other aspects of drug design including side effect prediction or multi-target evaluation related to a single disease [16]. Molecular docking was thus rapidly implemented into the search for potential COVID-19 treatment strategies once the structures of notable SARS-CoV-2 proteins were solved [17,18].

### Potential SARS-CoV-2 inhibitors from foods

Over the last few months, numerous studies have used molecular docking to screen food compound libraries for candidate inhibitors of SARS-CoV-2, albeit with different approaches. Several studies screened large databases of *ca.* 10 000 to over 162 000 food constituents for candidate compounds [19,20,21,22]. Casting a wide net allowed these researchers to identify specific chemical features that may be integral for strong association with the target substrate. For example, compounds that contained aromatic nitrogen atoms [20] and polycyclic structures were predicted to form strong associations with residues within the active site of SARS-CoV-2 main protease (M<sup>pro</sup>), a crucial protein of coronavirus replication [22]. Other researchers took a more targeted approach in their screening and focused on specific compound types when curating libraries of potential ligands. A common strategy was to screen compounds previously associated with antiviral activity, such as polyphenols. From these studies, polyphenols from green tea [23], pomegranate peel [24], honey and propolis [25]; flavonoids from citrus [26] and other sources [27,28]; and tannins [29] were reported to have high predicted potency against SARS-CoV-2 M<sup>pro</sup>.

Rather than focus on specific compound types, some researchers opted to conduct food-oriented exploratory expeditions. Such studies evaluated known compounds of specific foods such as spices [30,31], cinnamon [32],

olives [33], and teas [34]. Interestingly, a large number of studies evaluated foods that are traditionally associated with medicinal properties and ethnopharmacological usage. Authors of such studies screened libraries of compounds curated based on literature review or traditional knowledge [35–40], their presence in medicinal ingredients such as black cumin (*Nigella sativa*) [41,42], or chemical identification by chromatographic and spectrometric analyses of medicinal foods such as garlic oil, horchata, and Liupao tea [43,44,45]. The drug-likeness of highly ranked compounds was determined in many of these studies using *in silico* assessments of their pharmacokinetic and toxicological properties, with authors concluding that high-ranking compounds have potential for lead optimization into drug candidates and warrant further experimental validation, although such validation studies currently remain scarce. The identification of potential antiviral compounds from these studies were typically presented as supporting evidence for the purported antiviral activities of the food sources.

Food compounds that exhibit non-antiviral biological or functional properties were also curated and assessed for potential activity against SARS-CoV-2. Wahedi *et al.* [46] evaluated stilbenes, which are associated with anti-tumor, anti-inflammatory, and other biological activities, with the aim of repurposing them as agents against COVID-19 and found that resveratrol may have potent activity inhibiting the host-virus interactions mediated by SARS-CoV-2 spike protein. Food-derived peptides with purported anti-hypertensive activity were predicted to interact with various targets of SARS-CoV-2 and demonstrated potential as lead compounds for COVID-19 treatment [47]. Nisin, a well-established and common food preservative with known antimicrobial activity, was reported for the first time to potentially possess antiviral activity via interactions with human angiotensin-converting enzyme 2 (ACE2), a protein involved in coronavirus-host recognition [48]. These studies mirror pharmaceutical drug repurposing research, which seek to identify new therapeutic uses for drugs that are already extensively studied, approved, or discontinued. By taking advantage of the research and development already conducted on existing compounds, drug repurposing expedites the search for new drugs. Considering the examples listed above, it is possible, then, that repurposing studies on food ingredients and approved additives may also help expedite the search for new bioactive food ingredients.

### Proteins may release antiviral peptides after digestion

In contrast to treating food as a cornucopia of potentially therapeutic compounds as described above, some researchers have sought to screen for compounds that may be released by digestive enzymes after consumption. Studies using this approach assessed bioactive peptides

released from dietary proteins from grains, seeds [49,50], and microalgae [51]; fish [52] and squid [53]; and soy cheese [54<sup>•</sup>]. While some studies followed the modern omics approach, wherein peptides are first isolated and identified *in vitro* using liquid chromatography and mass spectrometry [49,54<sup>•</sup>], most of these studies adopted an entirely *in silico* approach that used simulated gastrointestinal digestion to predict the resulting mixture of hydrolyzed peptides. Also unlike contemporary bioactive peptide research, which typically focus on peptides as a purified end product [9], several studies listed here also considered the applicability of the source protein as nutritional interventions for COVID-19 patients [50–53]. Aside from peptides, intact proteins from bee-secreted royal jelly with antiviral activity against Hepatitis C and B viruses [55] were also predicted to associate with several SARS-CoV-2 and host targets [56], although the mode of delivery of these proteins for COVID-19 remains to be explored.

### Links between diet and COVID-19 susceptibility

The use of molecular docking in food and nutritional sciences to explain or theorize relationships between diet and disease susceptibility has emerged during the pandemic. When epidemiological analysis revealed that countries with marine-sourced dietary omega-3 fatty acids had lower fatality rates of COVID-19, Vivar-Sierra *et al.* [57<sup>•</sup>] used molecular docking results to help propose that a possible explanation was impeded host entry due to omega-3 fatty acids reinforcing the closed (i.e. inaccessible) conformation of the SARS-CoV-2 spike protein. Chowdhury *et al.* [58] used molecular docking to suggest that the strong association predicted between choline and SARS-CoV-2 M<sup>Pro</sup> could help explain earlier observations that higher choline levels in expecting mothers who were infected with COVID-19 may have protective effects for fetal brain development. As a final example, Wang *et al.* [22<sup>•</sup>] postulated that the higher consumption rates of beer and tea, both of which they reported as sources of potentially potent SARS-CoV-2 M<sup>Pro</sup> inhibitors after screening 10,870 food compounds, may play a role in the fast recovery of Germany and China, respectively, after their initial waves of COVID-19.

### Critical interpretation of results

Although the recent increase in docking research led to some compounds being evaluated in multiple studies, direct comparative analyses of results among studies are rare [52,59] and challenging due to differing methodologies [60<sup>•</sup>]. For example, although Rout *et al.* [31] and Ibrahim *et al.* [37] both evaluated the ginger compounds gingerol, shogaol, and zingerone against M<sup>Pro</sup>, their use of different docking software and starting protein structures may contribute to their discrepancies in ranking: while the former study scored these compounds closely (−5.8 to −6.1 kcal/mol), gingerol and shogaol were scored higher

(−7.1 and −7.4 kcal/mol, respectively) than zingerone (−5.7 kcal/mol) in the latter study. Further, while both studies scored the former two compounds lower than capsaicin and piperine, the analysis by Umesh *et al.* [30] scored them both higher.

When interpreting recent study findings, another aspect to consider is how the molecular docking results were processed. While many studies discussed in this review aimed to identify lead compounds for optimization into potent drugs using molecular docking as a primary method, computer-aided drug design often implements molecular docking into longer workflows with pre-docking and post-docking data processing using molecular dynamics, artificial intelligence, statistical methods, and other methods to improve the accuracy of obtained results [16]. Molecular docking itself also undergoes constant improvement in pharmaceutical science, exemplified by recent advances in dataset benchmarking and the use of consensus scoring or machine learning for more accurate results [61]. Although some of the studies in this overview included molecular dynamics as a post-docking assessment, many lack additional data processing steps. The short production times of molecular dynamic simulations used in some studies also risk missing important changes in binding stability [43,47,58], changes of which occur over timescales of 100–200 ns [19,22<sup>•</sup>]. Specific workflows may also be required depending on the analytes evaluated. For example, a rigorous filtering protocol with positive and negative controls can mitigate false positives when screening flavonoids [60<sup>•</sup>].

Beyond experimental set up, the results obtained from molecular docking studies must also be contextualized by the narrow scope of the analysis. For example, while molecular docking can predict direct interactions between food constituents and disease targets with high precision, actual nutritional modulation of the body's response to disease may extend beyond such associations and involve complex cell signaling pathways that cannot be inferred from docking results alone. The protein structures used may also lack physiological context, such as the glycan shielding and crowding effects on SARS-CoV-2 spike protein [62]. Furthermore, the typically low bioavailability of high-ranking compounds has cast doubt on the applicability of recent study findings [63], although some researchers have proposed that active compounds be incorporated into nanoparticles or pharma-nutraceutical formulations to improve uptake [35,64<sup>•</sup>] or administered as throat rinses [53]. Docking studies alone also provide minimal insight on the dosage required of a compound to elicit physiological or temporal effects.

Despite the limited scope of standalone studies, the recent increase in docking studies facilitate the observation of general trends. For example, many highly ranked

compounds with predicted inhibitory activity against M<sup>pro</sup> contain polycyclic structures [22<sup>•</sup>,31,33<sup>•</sup>] or, in the case of peptides, amino acid residues containing ring structures [50,53]. Compounds such as epicatechin and its derivatives [23,27,44<sup>•</sup>] and hesperidin were also consistently ranked highly as candidate inhibitors of various targets involved in SARS-CoV-2 infection and replication [36,40,64<sup>•</sup>,65<sup>•</sup>]. Reviewing the results from multiple studies can provide additional context for the findings from standalone studies. Fatty acids, for example, may still offer protective roles against COVID-19 despite low predicted association with SARS-CoV-2 M<sup>pro</sup> [22<sup>•</sup>] by complexing with other viral targets [57<sup>•</sup>]. Similarly, although organosulfur compounds such as diallyl disulfide and diallyl trisulfide from garlic scored relatively low among spice compounds for M<sup>pro</sup> [30,37], further investigation into these compounds may still be warranted due to their abundance in garlic oil — together accounting for over 51% of constituents — and predicted interaction with ACE2 [45].

### Translatability of findings

While examples of translatability between molecular docking results and clinical effect exist in drug discovery [15], such translations for food components and disease are less abundant. Epicatechin and its derivatives [27,44<sup>•</sup>] and high-ranking flavonoids [28] were reported to exhibit potent *in vitro* inhibitory activity against M<sup>pro</sup>. The antiviral activity of hesperidin against SARS-CoV-2 [65<sup>•</sup>] and hepatitis A virus as a model RNA virus has also been demonstrated in cellular and plaque assays, respectively [64<sup>•</sup>]. Considering these limited examples and past research on the antiviral activities of polyphenols [5], the results reported from recent docking studies may be translatable to *in vitro* experimental results at least for some plant compounds. However, the *in vivo* inhibitory activity of food components against SARS-CoV-2 remains largely unknown since suitable animal models for COVID-19 remain under active development [66,67]. It is thus difficult to fully assess the applicability of recent findings on the treatment of or protection against COVID-19 at this time.

Even considering the lack of research evaluating the nutritional and clinical contributions of recent molecular docking studies on food components, the increased use of molecular docking in food research has demonstrated the practicality of this method for enriching discussions of food and its effects on disease susceptibility. Using COVID-19 research as a case study, it becomes evident that molecular docking allowed researchers to respond very quickly to an urgent global health issue and contribute to conversations of diet-disease relationships by conducting large-scale screening of food antivirals for drug development, exploring nutritional intervention strategies, and searching for the molecular basis behind epidemiological trends. Such conversations will become ever

more important as the search for treatments against SARS-CoV-2 continues and the world seeks to prepare for post-pandemic normality. Already, evidence linking plant-rich diets with protective effects against COVID-19 is mounting [3,4]. Deficiencies in certain vitamins and micronutrients have also been associated with increased COVID-19 hospitalization and mortality, and the applicability of these nutrients as interventional strategies may become clearer as more data is collected from ongoing clinical trials [2]. While further validation studies are still required to demonstrate clinical effects, the critically interpreted results from molecular docking studies can provide insights to guide subsequent research and a starting point for theorizing diet-disease relationships. These recent trends may thus provide impetus for future antiviral and bioactive food research to continue leveraging molecular docking when applicable. Whether the recent widespread utility of this method is an artefact of a severe pandemic, however, or signals new opportunities for bioactive food research remains to be seen.

### Conflict of interest statement

Nothing declared.

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