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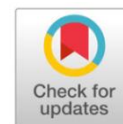## *An Overview of the Curcumin-Based and Allicin Bioactive Compounds as potential treatment to SARS-CoV-2 with structural bioinformatics tools*

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Abstract: The recent outbreak of SARS-CoV-2 across the globe and the absence of a specific cure against the disease lead the scientific community to investigate some alternative indigenous treatments. SARS-CoV-2 is the virus responsible for the coronavirus ailment 2019 (COVID-19). This virus has 4 auxiliary proteins namely the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins. The main proteases and RNA dependent RNA polymerase are also essential structures by which the virus replicates and survives. Each of these proteins are structures of the virus that are potential targets for drugs which are leads in the drug discovery process of any drug for the virus. Currently available treatments are not specific to the disease and therefore carry unwanted adverse effects that can be highly dangerous and sometimes fatal. Many of these treatments are supplementary in nature or based on repurposed drugs from other viral outbreaks. Alternatives of conventional drugs are required to control the spread and severity of the disease. Allicin, curcumin and their derivatives have been researched for their antiviral property and shown to have good binding affinity towards SARS-CoV-2 structures essential in their survival, especially the main proteases and RNA dependent RNA polymerases. The structural bioinformatics tools have elicited methods to predict the bioactivity of the natural product-based compounds. Apart from the beneficial medication that they offer, natural products carry along other advantages for the current pandemic situation in terms of supply, logistics, and affordability.

Keywords: Bioactive Compounds; Coronavirus; COVID-19; *In Silico*; SARS-CoV-2.

INTRODUCTION

The outbreak of SARS-CoV-2 that began in Wuhan, China has spread to virtually all parts of the world[1]. Numerous people have been infected and a portion have also died. The status of pandemic has been declared for this virus outbreak with nations that unable to control the spread and mortality of their own population. The discovery and production of vaccines remains the only effective method of reducing deaths and severe cases during the pandemic. Several companies have developed and gotten authorization for use by the general public in the past year including Pfizer, Moderna, Sinovac, Johnson & Johnson among

others[2]. Despite being able to provide protection against the virus with their own efficacy rates, vaccines are only able to contain infections and minimize symptoms which is not a cure against the disease itself[3].

Antiviral drugs are a class of drugs that can treat and cure viral infections[4]. Until today, there are no antiviral drugs that specifically target SARS-CoV-2 and cures the associated disease. All attempts at using antiviral drugs are repurposed medications that are meant for other infections, of which include Remdesivir that was proven effective and used in the Ebola outbreak[5]. However, repurposed drugs have their own drawbacks against the novel coronavirus in the form of adverse effects that range in severity and forms[6,7]. The costs associated with these medications are also not cheap, especially in a prolonged period of infection. Alternatives that are both safer and more affordable would provide substantial benefit towards the treatment of SARS-CoV-2 where it could reach more people, including those with less financial capabilities and therefore reduce severe cases or even mortality rates[8].

Natural products derived from plants are abundant in countries rich with spices such as Indonesia, Southern China, and India[9]. Local people of such countries have deep inclinations toward the use of traditional herbs and plants as treatments for all sorts of illnesses[10]. When studied further, traditional medications may contain properties that are associated with antiviruses. Some of which may have been used to treat virus infections effectively in the community. In addition to effective treatments, there are other advantages that these natural products bring such as the readily massive supply for the product as well as the significantly lower costs compared to pharmaceutically produced medications such as remdesivir and biosimilars such as plasma convalescent therapy[11]. A favorable alternative may be present in one of these natural products and this review paper aims to identify natural products that have the potential to treat SARS-CoV-2 and can provide an alternative against current pharmaceutical drugs.

OVERVIEW APPROACH

Keywords were selected based on their relevance to the main aim with specific attention to allicin and curcumin compounds and its effects on the SARS-CoV-2 virus, especially for the main proteases and RNA dependent RNA polymerase structures. By using the keywords, such as SARS-CoV-2, Main proteases, RNA dependent RNA polymerase, allicin, curcumin, *In silico* drug design, and Docking, independently or in conjunction with each other in various orders through NCBI, literatures were founded in their Pubmed Central (PMC) database in https://www.ncbi.nlm.nih.gov/pmc/. The journals used for the topic foundation were collected and selected with publication dates ranging between 2020 - 2021. Other supporting literature from outside the range have also been included for its merits in justifying the findings.

RESULTS AND DISCUSSION

SARS-CoV-2 is the virus responsible for the coronavirus ailment 2019 (COVID-19). It has 4 auxiliary proteins namely the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins. Each of these proteins are structures of the virus that are potential targets for drugs which are leads in the drug discovery process of any drug. The virus also has two other structures that are highly influential in their replication process, the main protease and RNA-dependent RNA-polymerase (RdRp). Main proteases in beta-coronaviruses are distinct to human proteases which acts as a potential drug target that does not interfere with other human cellular activities. The function of the main proteases of beta-coronaviruses is to exclusively separate polypeptide sequences through cleaving and the section that this occurs is specifically after a glutamine residue.

This substrate specificity is not found in human host-cell proteases[12]. On the other hand, the RNA-dependent RNA-polymerase found in SARS-CoV-2 is crucial in the transcription and replication of the viral genome[13]. Since the process of replication and viral transcription is essential to the virus survival, it is an obvious drug target for many drug developments. Attempts in finding a cure or vaccine have been directed towards the 4 auxiliary proteins and the two important proteins, main proteases and RNA-dependent RNA-polymerase since it is believed that these structures hold key roles in the virus infection process.

Currently the treatment of COVID-19 has relied heavily on the symptoms and complications that the disease brings along. In most cases, the basic treatment includes providing medical support in the form of oxygen and fluid supply and antibiotics for secondary infections. Several vaccines have also been developed and approved for public administration including that from Pfizer, Moderna and AstraZeneca. However, a vaccine does not cure an infected person rather it prevents severe symptomatic cases from occurring. A cure ideally needs to have the property to inhibit and cease the replication process of the virus within the body. No such medication has been discovered for COVID-19. The WHO has supported clinical trials for the use of drugs against the disease by using repurposed drugs that are meant for other illnesses including that of remdesivir, chloroquine, hydroxychloroquine, and dexamethasone. As these drugs are not specifically developed for COVID-19, there are adverse effects that need concern. Remdesivir is administered intravenously and was used previously in the Ebola virus outbreak. It can inhibit virus replication however results from clinical trials have shown that the faster recovery experienced by patients was not significant enough to be considered effective. The drug is also currently undergoing an Adaptive COVID-19 Treatment Trial 3 or ACTT3 with Rebif. Chloroquine and hydroxychloroquine are malarial drugs that have no significant observed benefit towards COVID-19. In addition, the drug also has concerns of inducing cardiac problems in infected patients. Dexamethasone is a glucocorticosteroid meant to treat inflammation that is also used in cancer treatment and prevention[14]. Together with the use of ventilators or oxygen supplementation, dexamethasone has been observed to increase mortality rates among patients[15].

Medications derived or based on natural products are promising in terms of its supply, safety, and effectiveness. It has also been used by communities and passed down for generations as folk medicine. Additionally, natural products are often present in massive supply and are readily available to large populations and possibly without the need of production. Commonly used natural products for illnesses are endophytes and medicinal plants in which some may contain antiviral properties against various viruses. A medicinal plant called theaflavin has been observed to be able to inhibit RdRp and suppress COVID-19[16]. Likewise, allicin and curcumin have promising properties against the virus that is shown by their high binding affinity to both the main proteases and RdRp[17]. Allicin and curcumin are compounds that are present in common kitchen ingredients known as garlic and ginger, respectively. The commonality of these products provides a potential that exceeds manufactured drugs where it can reach people in a wider range of economic categories with ease compared to costly patented drugs. The table 1 briefly describes the medicinal properties for both the compounds.

There has been research and clinical trials that are conducted using both compounds and their derivatives. Most of the research has been done through means of *in silico* methods, especially molecular docking. A research study has identified the potential use of organosulfur compounds, which includes allicin, and flavonoids for their immunomodulatory effects. Immunomodulatory compounds can stimulate or inhibit the body's immune system against diseases and infections. The effects have supported the study's conclusion of organosulfur

and flavonoid's ability to reduce viral infections against SARS-CoV-2[18]. Another research has identified another potential drug candidate through *in silico* molecular docking targeting the SARS-CoV-2 spike protein or also known as the S auxiliary protein. The identified compound is a curcumin derivative, called Bis-demethoxy curcumin, which was observed to have a high binding affinity towards the viral spike protein[19]. This spike protein is essential in the virus infection process when entering a host and inhibiting such mechanisms would hinder the virus survivability. Despite the research showing positive results, it has not been proven in real-life situations and therefore, clinical trials would be required to validate the findings and assess its significance as a drug candidate. Some drugs that are based on curcumin and its derivatives are in the process of clinical trial research. One of these clinical trial researches is for the oral spray "ArtemiC®", which is based on curcumin and artemisinin compounds. The research was conducted in collaboration between MGC Pharmaceuticals and a Swiss firm, Micelle Technology and it has progressed to complete Phase II of clinical trials with diagnosed COVID-19 patients located in India and Israel[20]. Another study conducted by the Isfahan University of Medical Sciences in Isfahan, Iran has gained approval for clinical trials and will commence its recruitment process. Their drug candidate is a co-supplementation of curcumin and piperine which aims to determine the efficacy on the recovery process on COVID-19 diagnosed patients.

Table 1. Description of the medicinal properties for allicin and curcumin compounds.

No.	Allicin	Curcumin
1	Functional food, well known for its immunomodulatory, antimicrobial, antitumor properties, etc.	Curcumin can address a wide scope of potential applications, such as pain management.
2	Able to decrease the concentration of leptin.	Capable of boosting natural immunity and protective defense.
3	Decreases the levels of leptin, leptin receptor, and PPAR-γ.	Good tolerability and safety profiles have appeared in clinical trials.

In order to develop the treatment of coronavirus, a new conventional drug is needed, that drug is Remdesivir. In the latest research on conventional drug, remdesivir, which is a nucleotide analogue prodrug that perturbs viral replication, has been evaluated in clinical trials to thwart the Ebola threat in 2014[21]. Among the candidate therapies, remdesivir has shown efficiency in both in vitro and in vivo against coronavirus, however a much-needed clarity surrounding the repurposing of the approved drugs and experimental agents against coronavirus is needed. In the research, there are two proposed for the alternative treatment, the natural treatment, and the conventional drug. The natural treatment is based on the plant-based treatment. The components used in the natural treatment are garlic and turmeric. Garlic and turmeric have been alleged as an effective cure against the coronavirus disease. Garlic contains the sulfur phytochemicals that provide anti-inflammatory, antitumor, substantial immunomodulatory, and cardioprotective features[18]. The components inside the garlic such as S-allyl cysteine sulfoxide (alliin), ajoenes (E- and Z-ajoene), vinyldithiins (2-vinyl-(4H) - 1,3-dithiin, 3-vinyl-(4H)-1,2-dithiin), and diallyl (di and tri) sulfide allow the garlic to counter back the virus threats. In the latest research, researchers have found the structure of the the main protease of the SARS COVID-19, a serine-type Mpro (chymotrypsin-like protease (3CLpro)) protease with the kind of amino acids (such as Thr24, Thr26, and Asn119) near the active site. Since the protease is responsible for virus replication and because of proteolytic maturation of the covid, the infection rate might have decreased due to the hindering the cleavage of the viral polyprotein. As for the other natural treatment, turmeric has been used in the old/traditional medical way and an integral part of Asian cooking. Turmeric

(curcumin) managed to prevent influenza A-virus injury by blocking the nuclear factor kB signalling and inhibiting the inflammatory cytokines. The role of turmeric in repressing the inflammatory process might be helped in preventing the Covid disease[22]. Drugs derived from the natural resources as bioactive antiviral compounds have more potential to cure coronavirus infection as compared with other synthetic drugs with less side effects. Finally, the conventional drug, Remdesivir. Remdesivir is an antiviral drug, used to de-accelerate the RNA viral infections of SARS-COV2. It was reported by researchers on the successful recovery of COVID-19 patients by using remdesivir[23]. Nevertheless, treating severe coronavirus patients with remdesivir has not shown good responses.

The structural bioinformatics tools might assist to find the favorable natural product leads to inhibit the SARS-CoV-2 virus[24]. It would require two essential instruments, namely the natural product database and the necessary software[25,26,27,28]. The pipeline is comprises on these steps: Sequence analysis, protein structure analysis, QSAR analysis, Protein Docking, ADMETOX, and molecular dynamics simulation[29,30]. The protein-ligand complex as the result of the pipeline is shown in the figure 1. It elicited the attachment of the ligand into the cavity of the protein based on the most favorable binding energy. The tools are easy to use, straightforward, and could assist wet laboratory research accordingly[31].
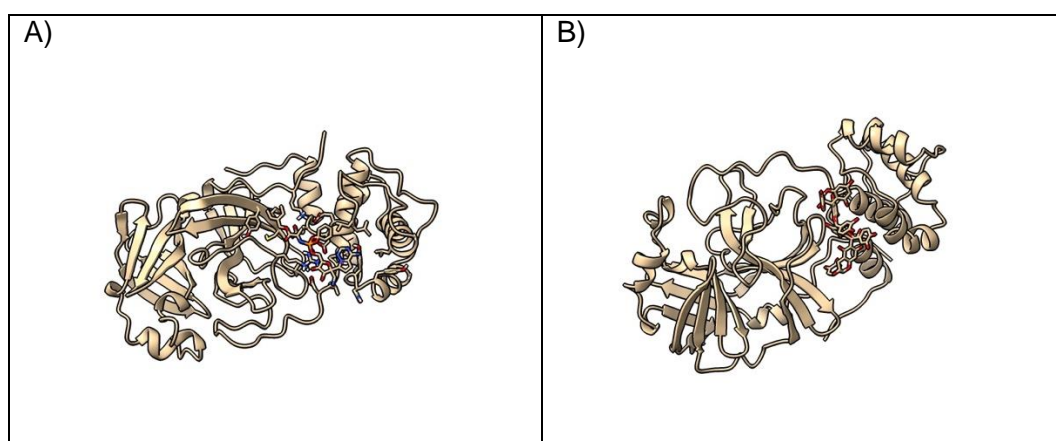

Figure 1. The 3D visualization of 3CL-protease SARS-CoV-2 protein complex with a) remdesivir b) Chemspider compound ID: 17337318 from the SARS-CoV-2 virtual screening research[32,33].
Note: Images were depicted with ChimeraX software and reproduced with the permission of the corresponding author on behalf of others[34].

For the future prospect, plant-based medicine might be very valuable. Regarding the market, the plant-based medicine might be low cost compared to the conventional drugs. Allicin and Curcumin can be easily manufactured and made available due to its natural raw material. In addition, the nature of allicin and curcumin were have well immunomodulatory, antimicrobial, anti-inflammatory, antimutagenic, antitumor properties, it makes Allicin and curcumin can be developed further for other viruses in the Coronavirus family and may be repurposed for treatment against other viruses. According to researchers, by using the pharmacoinformatic and hypothetical studies on allicin and curcumin, with in-vitro (In vitro assessment of protease inhibitory properties) and in-silico (Molecular docking and molecular dynamics) techniques, stated that the allicin and curcumin were revealed to occupy the binding site comprising of GLY-143, SER-144, CYS-145, and HIS-172[35]. By that, it means that curcumin has appreciable binding affinities cathepsin K, COVID-19 main protease, and SARS-CoV 3C-like protease which are all target proteases involved in viral entry. Thus, the binding of allicin and curcumin could influence the conformational dynamics

encoded in the structures of the proteases and subsequently their respective functional properties and innate capability to potentiate the pathogenesis of coronavirus. This observation could substantiate use of phytochemicals as therapeutic agents based on their target specificities and potencies[36,37,38]. However, this potential medicine should be most applicable to countries with a large supply of spices such as India and Indonesia. Other countries would benefit as well. Another benefits, by this proposed treatment, some things that indeed to be taken care more such as method of disease containment while awaiting vaccine rollout, minimize casualties, help recovery of patients resulting in immune system development, might not require trained practitioners to administer, distribution can be faster as requirements are less (i.e., freezer and security), quicker treatment for remote areas and with minimize cost already observed well. Nevertheless, in this paper, based on the molecular docking result, it is shown that allicin and curcumin could have potential to become the medicine of COVID-19, further clinical experiments were needed to elaborate and validate the statement more, and to develop the competent medicine for the future.

CONCLUSION

The COVID-19 has become a recognized and concerning global pandemic which has affected whole nations around the world, an unorthodox alternative solution for a cure is needed to slow down the virus threat whilst pharmaceutical companies continue their efforts. Scientists all over the globe have been racing to find the cure as soon as possible so cases and casualties will be minimized. Research on natural compounds has identified 2 potential alternatives, curcumin-based and allicin which has been observed through in silico methods for their high binding affinity towards SARS-CoV-2 structures and antiviral properties. The potential for both compounds can extend beyond its medicinal benefits and into other factors of concern such as logistics, supply, and safety. Countries with an abundance of spices would primarily benefit from this discovery, if proven effective, though it does not limit other countries from reaping the benefits. Likewise of conventional medicine, natural products may also be capable of treating other concerning viruses in the larger betacoronavirus family or even beyond. Clinical trials are highly required in the validation of these findings to identify certain obstructions of their benefits and would likely play an important role for natural products to proceed further against SARS-CoV-2 and subsequently COVID-19.

AUTHORS' CONTRIBUTIONS

All authors contributed equally to this work.

DATA AVAILABILITY STATEMENT

The utilized data to contribute to this investigation are available from the corresponding author on reasonable request.

DISCLOSURE STATEMENT

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the

authors. The data is the result of the author's research and has never been published in other journals.

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