

Ideas and Activities of Developing Drugs For COVID-19: A Review

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ABSTRACT

This article has been produced by reviewing various review and original articles published recently with the subject matter of developing drugs for COVID-19 infection. Most of the articles reviewed are the results of *in vitro* and *in silico* investigations. The outcome of the rereview is rudiment. It focused on the use of AYUSH-64 in COVID-19 patients together with standard care for early recovery and better outcome. The other focus was on the possible application of an ancient Ayurvedic formulation combined with lauric acid for application at the nasopharynx to mitigate the severity of highly infectious COVID-19 infection.

REREVIEW

Nature [1] reported the fading hope of achieving herd immunity to the COVID-19 infection. It becomes imperative to consider the methods other than the vaccination, though necessary to support the efforts to produce better vaccines. It may also be considered that both the vaccination and other preventive methods of COVID-19 infection and treatment have to go concurrently. This has inspired the authors to rereview the present status of the search for alternative methods of preventing/treating COVID-19 infection.

There has been a spur of research activity towards finding solutions for the COVID-19 pandemic ever since its emergence. It has provoked and promoted an unnatural boom in anti-viral research, with the realization of the lack of targeted medicaments and vaccines. Until June 2021 there were more than 100,000 Google searchable entries with the keyword 'COVID-19' or 'SARS-CoV-2'. The majority of such publications were the reports of *in silico* molecular docking of bioactive phytochemicals against the virus, targeting the virus proteases, spike glycoproteins and RNA-dependent RNA polymerase, and host-specific angiotensin-converting enzyme 2. A great majority of the results were of phytochemicals either from rudiment data of traditional medicines or chemical databases. Some are described below:

Authors have examined [2] the potent phytochemicals against COVID-19 infection from Phyto-materials used as antivirals in alternative/complementary medicines. Efforts have been made to find how COVID-19 like symptoms were managed in the past by mining the classical literature of systems like Ayurveda and Chinese traditional medicine and evaluated them by contemporary scientific methods. For example, they have studied [3] the compounds of *Citrus*

medica and *Zingiber officinale* for COVID-19 inhibition in the light of cues from Ayurveda. They have done [4] an excellent effort to compile a great amount of data on the possible cures of COVID-19 infection. It is a compilation of data from all schools of medicines, without a concrete recommendation as sounded in the title of the article. Most of the efforts to find sure solutions were like solving it by trying to arrange jigsaw pieces for making an unknown picture, based on contemporary research. This effort fails the traditional wisdom of a specific formulation where the role of each herbal component is seldom described in the medical classics, though there may be success to certain extent if resorted to the format of the traditional medicine. Only one article has been located with a comprehensive analysis of a complete traditional medical formulation for managing COVID-19 like symptoms [3]. The Ayurvedic formulation has been in use for millennia as an application at the nasopharynx to mitigate the severity of highly infectious fever and other symptoms similar to COVID-19 infection. The above cue was tested *in silico*. It was found that the phytochemical compounds in *C. medica* and *Z. officinale* may have good potential in reducing the viral load and shedding of SARS-CoV-2 in the nasal passages. They

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reported [5] that AYUSH 64, a poly-herbal drug formulated in the last century based on traditional knowledge of Ayurveda and had been in use for various clinical conditions of influenza-like illness, found safe and efficacious in COVID-19 patients along with standard care for early recovery and better outcome. Several articles report on medicinal plants and their compounds, without specific traditional background information for combating symptoms similar to COVID-19 infection. However, they could also be of great use. Accounts, featuring the salient features of some reviews are given below.

Bellavite [6] focused on the protection against COVID-19 infection indirectly with hesperidin and quercetin, the acclaimed components of some nutraceuticals. They have a complex mechanism of action, involving both cellular defense against oxidative stress and the modulation of inflammation. Theirs is a defense, repair and activation mechanism of the immune system. They can have indirect effects in infectious, respiratory diseases as they prevent or improve metabolic and vascular comorbidities which complicate the clinical course of COVID-19 infection.

Alkaloids are one of the most widespread plant-derived natural compounds with pronounced antiviral effects. Accordingly, these phytochemicals have been proposed as promising candidates for discovering effective treatments for COVID-19. Alkaloids have shown potential anti-SARS-CoV-2 activities by inhibiting pathogenesis-associated targets of the Coronaviridae family. A review [7] reported extensively on *in vitro* inhibitory effects of many alkaloids on different viral pathologies, with the result of *in silico* interactions with target proteins in some cases.

There is a plethora of studies that demonstrates the inhibition of Spike-ACE2 interactions to impair COVID-19 infection. A selective pick from the compounds of the traditionally used herbs and documented as contemporary literature has enabled [8] to propose hits that are highly promising out of stringent *in silico* checkpoints. They [9] have produced a representative investigation of *in silico* methodology by searching extensively to predict that the phyllaemblicin and cinnamtannin class of phytochemicals could be potential inhibitors of both the spike and Mpro proteins of SARS-CoV-2. Furthermore, they have included pharmacology and clinical optimization in their report to lead towards novel COVID-19 small-molecule therapy. They have exploited [10] the natural bioactive compounds from medicinal plants that inhibit the platelet mediated thrombus formation which could be proposed for the treatment of SARS-CoV-2 infection. They have reviewed [11] the immense potential of computer-aided drug design for managing COVID-19. They have focused [12] their study on the relevance of utilizing natural lead molecules by virtual screening and pharmacokinetics prediction for developing drug leads against SARS-CoV-2. They exemplified [13] the phytochemicals from selected traditional herbs used in

traditional Indian medicine having significance in steam inhalation therapy for COVID-19. However, none of these studies evaluates any specific, traditional formula. Instead, they focus on the raw herbal drug materials in a system-free analytical regime.

Earlier studies of medicinal plants have shown promising anti-viral properties and beneficial, multiple applications for health-related issues. Such plants are being used by traditional practitioners to protect from various health problems of humans and animals [14-16]. They have compiled the data of the Mechanism of antiviral action of phytochemicals, which include quercetin, apigenin, baicalin, luteolin and sulphated polysaccharides and their derivatives. They have noted [18] that antiviral polyphenolic compounds such as betulinic acid, indigo, aloe emodine, luteolin, and quinomethyl triterpenoids, quercetin or gallates can inhibit coronavirus enzymes, which are essential for virus replication and infection.

A review performed that [19] brought out the use of certain medicinal plants to treat COVID-19 infection and drew attention towards investigating potent chemical constituents from medicinal plants, specifically *Andrographis paniculata* profusely used in the system of Ayurveda. It has shown strong antiviral activity against different classes of viruses, such as influenza virus, hepatitis B virus, herpes simplex virus Etc. They proposed [20] innovative antiviral formulations and their bioactive compounds that could be useful toward the elaboration of anti-COVID-19 formulations. They have studied [21] the phytochemicals from three selectively picked medicinal plants to reutilize them for drug development against COVID-19 upon suggestions based on *in silico* studies. They have shown [22] that many plant extracts have emerged to have broad-spectrum antiviral activity and *Nigella sativa* with potent anti-SARS-CoV activity. The authors of this article have also done a comprehensive review on the potent phytochemicals against COVID-19 infection from Phyto-materials used as antivirals in complementary medicines [2]. They have focused on the use of fatty acids for preventing the COVID-19 infection for the first time [2].

Nearly forty thousand citable entries are there that either directly or indirectly propose bioactivities of phytochemicals towards COVID-19 infection. These projections are based on molecular docking and docking with molecular dynamics simulation studies-based projections. Many of these results are exciting, though there is a high probability that exact results may not be available in *in vivo* situation. Also, there may be phytochemicals categorized as false positives, due to non-specific binding with multiple targets. Such a situation may arise due to various factors. Non-bioavailability may be a problem which requires solution. There may be highly unpredictable outcomes if the results of the *in silico* recommendation taken into *in vivo* situation and the main reason for such unpredictability would be

solubility/bioavailability of phytochemicals showing bioactivity by *in silico*. The problem of solubility/bioavailability of phytochemicals may be practically solvable by either delivering them to the target tissues or increasing their bioavailability by their controlled delivery in the form of nanoparticles, liposomes, micelles or noisome to restrict the effects to the target alone as is done especially in the cases of chemo preventive drugs [23]. Polyherbal formulations like Ayurvedic medicines have a built-in solution for increasing the bioavailability of phytochemicals. Ayurvedic medicines are formulated to solve the problem of solubility/bioavailability by the addition of 'trikatu' (dried ginger, black pepper and long pepper) to almost every formulation, which has been proven to enhance solubility/bioavailability of hydrophobic compounds [24]. The result of the rereview performed is the realization that there are exciting results from the investigations till now for pursuing further for finding drugs for COVID-19.

THE OUTCOME OF THE REREVIEW

The rereview-endeavor highlights the use of AYUSH-64 in COVID-19 patients together with standard of care for early recovery and better outcome [5]. Another highlight is the possible application of the ancient Ayurvedic formulation [3] combined with lauric acid [2] for intervention at the nasopharynx to mitigate the severity of highly infectious COVID-19 infection.

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