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The Role of Conventional and Alternative Therapy in the Treatment of Covid-19: A Review

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) is a pandemic disease that has resulted in high morbidity and mortality rates. Currently, there is no antiviral treatment or vaccine for COVID-19, with symptomatic management being the only available management. The objective of this review is to evaluate the role of the combination of conventional and alternative therapy as well as the treatments individually in managing COVID-19.

Methods: Three electronic databases including Google Scholar, PubMed (MEDLINE) and ClinicalKey were used to identify papers published in 2020 using the keywords 'COVID-19', 'conventional treatment', 'conventional therapy', 'alternative therapy' and 'treatment of COVID-19'.

Results: Conventional therapy which include Hydroxychloroquine, Azithromycin, Remdesivir and Favipiravir all show antiviral properties against SARS-COV2. In addition, alternative therapies such as honeybee products, Chinese Herbal Therapy, Nigella Sativa and Curcumin also demonstrate potent inhibitory activity against the SARS-COV2. Certain combination treatment of conventional and alternative therapy have shown a quicker symptom improvement and recovery rate compared to conventional therapy alone.

Conclusion: In conclusion, the combination of conventional and alternative therapy has shown to be a more suitable treatment option than conventional therapy alone. However, more rigorous randomized controlled studies should be conducted to not only further evaluate the efficacy but also the side effects, cost, availability, and its applicability to the wider general population.

Keywords
COVID-19, conventional therapy, alternative therapy, traditional therapy, and treatment of COVID-19

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has recently emerged as a pandemic disease that has affected millions across the globe (Ahmed et al., 2020). In December 2019, the first outbreak was identified in China in the city of Wuhan and presented with respiratory distress and severe pneumonia. The causative pathogen was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 has since then globally transmitted across numerous countries and resulted in high morbidity and mortality rates (Ahmed et al., 2020).

SARS-CoV-2 which was previously known as novel coronavirus (2019-nCOV) consists of a positive single-stranded RNA virus and belongs to the family coronaviridae. It has been found to spread between humans via respiratory droplets from sneezing or coughing (Harapan et al., 2020). Risk factors include chronic comorbidities such as cerebrovascular disease, diabetes, age and coinfections of bacteria or fungi. The pathogenesis in the host has been noted to involve mainly receptor recognition (Harapan et al., 2020).

COVID-19 causes symptoms which include fever, dry cough, dyspnoea, and myalgia. Less common symptoms involve haemoptysis, sputum production, confusion, sore throat, rhinorrhoea, chest pain and diarrhoea. Hypoxemia, Acute Respiratory Distress Syndrome (ARDS), septic shock, acute cardiac injury and acute kidney injury have also been reported as severe complications (Harapan et al., 2020). The diagnosis of COVID-19 comprises of multiple factors which not only include symptoms such as fever and cough but also any history of travel recently or exposure to sick individuals. Regardless of clinical signs and symptoms, a laboratory confirmation of SARS-CoV-2 infection is defined as a confirmed case of COVID-19 according to the WHO (Wenger et al., 2009).

Unfortunately, no antiviral treatment exists for COVID-19. Proposed management currently involves supportive therapy such as fluid management, oxygen therapy and antibiotic treatment if there is presence of infection. At present, there appears to be no available vaccine that has been approved for current use (Harapan et al., 2020). In addition, evidence from clinical studies on the treatment options or prophylactic measures in reducing mortality

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appears to be limited. Therefore, supportive therapy remains the mainstay of treatment. However, despite the lack of evidence we will attempt to gather information on the treatment options and evaluate them in order to decide the best treatment strategy to adopt in managing the disease. The combination of conventional and traditional therapy will be looked at as well as the role of the treatments individually. This paper will review these treatments in order to determine the most optimum management of COVID-19.

METHODS

A comprehensive search was conducted in the international scientific database on ClinicalKey, PubMed, and Google Scholar using the keywords 'COVID-19', 'conventional treatment', 'conventional therapy', 'alternative therapy' and 'treatment of COVID-19'. The literature search included various clinical studies, retrospective analyses, randomized controlled trials and cross-sectional studies published in 2020 regarding the treatment options used for COVID-19. These articles were mainly assessed on the validity of the study design, favouritism of the study design, both inclusion & exclusion criteria description, validity of outcome measures, and results presented and their significance.

The Effect of Conventional Therapy in the Management of COVID-19

Author	Study design	Group/Participants	Intervention	Duration	Result
Beigel et al. (2020)	Double blind, randomized, placebo-controlled trail	1063 patients	Compered outcome after uses of 200 mg (loading dose) on first day and 100 mg for another 9 days of Remdesivir with placebo	10 days	- Shorten recovery time in Remdesivir group - Remdesivir had a median recovery time of 11 days compared with 15 days in patients received placebo<0.001
ŞimşekYavuz and Ünal et al. (2020)	Cohort	53 patients	Uses of Remdesivir	Not stated	- clinical improvement was observed in 35 /53 patient (68%)
ŞimşekYavuz and Ünal et al. (2020)	Open label case-control study	36 patients	Uses of HCQ alone compared to HCQ combined with Azithromycin	10 days	- combination of HCQ with Azithromycin resulted in viral clearance in all of the patients while using HCQ alone resulted in viral clearance in only half of the total patients (p<0.001)
Z. Chen et al. (2020)	Randomized clinical trial	62 patients	Compared the outcome of patient who used standard treatment only with patient who used standard treatment with Hydroxychloroquine (400 mg twice for 1 day, 200 mg twice for 4 days)	24 days	- Patients received additional HCQ show reduced in the symptoms of pneumonia (Cough and Fever) compared to standard treatment alone
Chen et	Randomized	240 patients	To compare the	10 days	- Clinical recovery

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al. (2020)	clinical trial	N=120 (receive Arbidol (200mg-=three times daily)) N=120 (receive Favipiravir (1600mg twice on first day followed by 600mg twice/day) but only 116 is asses	outcome between patients who receive Arbidol and patient who receive Favipiravir		rate of day 7 does not significant different between Favipiravir group and Arbidol (P=0.1396) - Favipiravir showed shorter time of reduction of pneumonia symptom (cough and fever) (P<0.0001) - Adverse effect of Favipiravir (raised in serum uric acid) was observed
Cai et al. (2020)	Open label case-control study	80 patients	Compare outcome between patient in FVP arm who received oral Favipiravir (Day 1: 1600 mg twice daily; Days 2–14: 600 mg twice daily) plus interferon (IFN)-a by aerosol inhalation (5 million (IU) twice daily) with patients in control arm who received LPV/RTV (Days 1–14: 400 mg/100 mg twice daily) plus IFN-a by aerosol inhalation (5 million IU twice daily)	14 days	- FPV group showed shorter viral clearance median time compared to control group ,4 d and 11 d respectively (P < 0.001) - The FPV group also showed significant improvement in chest CT compared with the control group, (P = 0.004)

The Effect of Alternative Therapies in the Management of COVID-19

Author	**Study design**	**Group/participants**	**Intervention**	**Duration**	**Results**
Babaei et al., 2016	Randomised control animal study	256 Japanese quails	Ethanolic extract of honey, propolis, bee pollen and royal jelly	42 days	Quail chicks fed with propolis and pollen had significantly higher antibody titres against avian influenza virus (H9N2) compared to other groups with $p < 0.01$.
Shimizu, 2011	Animal study	Mice with type 1 herpes simplex virus	Brazilian propolis	6 days	significantly reduced virus titers without toxicity, immunological activity

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Uddin, 2016	Standard plaque assay		co-incubation of non-cytotoxic concentrations of bee venom with HSV viral suspension	-	9-fold reduction in the virus titre with $P < 0.05$
S. Khan, A. Kazmi, N. Bashir, R. Siddique	Randomized clinical trial	214 COVID-19 patients	QingFeiPaiDu herbal formula	3 days	total effective rate above 90% with 60% improvement in symptoms and imaging performance. Stabilised symptoms in 30% patients; 130 patients completely cured.
Lau, et al SARS	Randomised controlled study	16,437 hospital care workers (1,063 in the herbal group and 15,374 in the non-herbal group)	modified formula of YuPingFeng powder and SangJu decoction	-	none of the participants In the herbal group contracted SARS, while (0.4%) in the non-herbal group were infected with SARS (P=0.035)
Jing Chen, Shaowu Lin, Conway Niu and Qi Xiao	Randomised controlled study	200 COVID-19 patients	control group: Arbidol hydrochloride experimental group: combination of Arbidol hydrochloride and ShufengJiedu (SFJDC)	14 days	200 COVID-19 patients; 1/2 patients (control group) treated with Arbidol hydrochloride; the other 1/2 (trial group) treated with Arbidol hydrochloride combined with ShufengJiedu (SFJDC) for 14 days. On the 5^{th} day of treatment, results showed: inflammatory marker levels significantly lower in the trial group ($P < 0.05$), abatement of fever, leucocyte count and resolution of chest CT findings significantly higher in the trial group ($P < 0.05$), recovery rate significantly lower (80%) in the control group with ($P < 0.05$)
Sourav Das(2020)	Molecular Study	-	Curcumin	-	Curcumin(8.15kcal/mol) has higher binding affinity than hydroxychloroquine (7.75kcal/mol) towards major protease of SARS-CoV-2
FatemahBabaei (2020)	Animal Study	Mice	Curcumin (Reduces myalgia and fatigue)	-	Oral administration has anti fatigue function and improved physical function
“	Animal study	Mice	Curcumin (Antipyretic)	1 – 5 hours	(100mh/kg) has antipyretic effect in rats

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“	Randomized controlled trials	609	Curcumin	2 weeks to 8 months	Reduction in circulating interleukins and circulating IL-6 and TNF-α levels (p = 0.005)
“	Animal study	Mice	Curcumin (Antioxidant)		(200mg/kg) Reduce malondialdehyde level and recovers the levels of xanthine oxidase and total anti oxidative capacity in ventilator- induced lung injury
“	Animal study	Mice	Curcumin (bronchodilator)	15 mins to 3 hours	(2.5 and 5 mg/kg, intranasal) reduced bronchochonstriction in the mouse model of asthma
“	Vero E6 cell study		Curcumin (anti-viral)		Prevented the replication and inhibited 3Cl protease of SARS-CoV Has inhibitory effect against the cytopathogenic effect of SARS-CoV
EbrahimM.Yimer (2020)	Clinical Trial	30 post-menopausal women	Allium Sativum and Nigella Sativa seed (anti-oxidant)	2 months	Significant reduction in plasma malondialdehyde (MDA) levels with increased activity in erythrocyte glutathione peroxidase (GSH-Px) and superoxide dismutase
“	Clinical Trial	40 female patients diagnosed with Rheumatoid Arthritis	Nigella Sativa Oil capsules (Anti-inflammatory effect)	500mg twice daily	exhibited improvement in disease activity score compared to placebo($p<0.05$) -a noticeable improvement was displayed in number of inflamed joints, incidence of morning stiffness, and disease activity
Sajjad Ahmad (2020)	Clinical Trial	Egyptian patients who were infected with the Hep C virus	Nigella Sativa (anti-viral)	450mg thrice a day for 3 months	Improvement in the clinical condition of patients with decreased viral load, less oxidative stress
“	Clinical Trial	Positive HIV adult	Nigella sativa (Anti-viral)	10ml twice a day for 6 months	Seronegative in EIA Western Blot after 6 months
	Molecular Study		Dithymoquinone (DTQ) Thymoquinone (TQ) and few other active compounds found in Nigella Sativa		Dithymoquinone has the highest binding affinity (8.6kcal/mol) to ACE2 receptor

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Rameshwar.S Cheke(2020)	Molecular Study		Hydroxychloroquine Chloroquine		Hydroxychloroquine and Chloroquine exhibited binding affinity of 6.8kcal/mol and 7.1kcal/mol respectively

CONVENTIONAL THERAPY

REMDESIVIR

Remdesivir is a phosphoramidite that was originally known as an Ebola virus (EBOV) antiviral. It inhibits viral RNA-dependent RNA polymerase (RdRp) and prevents exoribonuclease, 17 viral to proofread causing a premature termination of viral RNA transcription. It also has a wide range antiviral activity against variety of virus families such as paramycoviridae, filoviridae, and coronaviridae.[1]Sheahan et al. (2017) stated that a study on a model of mice infected with Severe Acute Respiratory Syndrome (SARS) showed reduction of the virus in the tissues of the lung after administration of Remdesivir.[2]Remdesivir has been suggested as a possible therapy for COVID-19 as SARS-CoV and SARS-CoV-2 have a similar pathogenesis of. Therefore, numerous studies on the use of Remdesivir have been conducted to assess the effectiveness of Remdesivir against SARS-CoV-2,

In another study, a patient from the United States was successfully treated on day 7 of hospitalization for progression of pneumonia using Remdesivir[1]. This was evident from the improvement of patient's condition where patient is afebrile, improved oxygen saturation to 94-96% in room air and chest X-ray showed absent of opacity on bilateral lower lobes of lungs.[3] Other than that, Beigel et al. (2020) conducted a study on 1063 patients infected with COVID-19 for ten days using randomized and double-blinded technique with placebo as a control. 541 patients were treated with 200mg Remdesivir on the first day followed by 100 mg for the next consecutive day. 522 of the patients were given a placebo during the study. This study found that patients with Remdesivir showed shorter recovery time than the placebo with 11 days (CI 95%, 9 – 12) and 15 days (CI 95%, 13 – 19) as the median recovery time respectively. In conclusion, the rate ratio recovery is 1.32, with CI 95%, 1.12 – 1.55 (p-value less than 0.001). [4]Other studies that have looked at reducing mortality rate with Remdesivir were also conducted. In a study of 53 patients , the use of Remdesivir reduced the mortality rate in 34 patients of whom require mechanical ventilation at baseline [5]. Although this drug has shown to be able to reduce the recovery time and mortality rate, it has a few adverse effects such as hepatic toxicity (increase transaminase) , kidney injury, nausea, vomiting and rectal haemorrhage. [1]

HYDORXYCHLOROQUINE

Chloroquine and hydroxychloroquine (HCQ) are an antimalaria drug with broad-spectrum activity against various viruses and the latter commonly used in rheumatoid arthritis and Systemic Lupus Erythematous.[1] These drugs act on the receptor pathway of the virus by interfering with the terminal glycosylation of Angiotensin-converting enzyme 2(ACE-2) receptor. It also prevent the membrane fusion of the virus and host cell by increasing the pH of endosome [6]. The mechanism of action of these drugs shown the capability of the drug to act against SARS CoV-2 virus. Therefore, a few studies were conducted to demonstrated the efficacy of drugs against COVID-19.

An in vitro experiment between chloroquine and hydroxychloroquine showed that hydroxychloroquine is more potent in inhibiting the production of mRNA of SARS-Cov-2.[7] It was demonstrated by the lower EC50 value in HCQ (0.72 μM) compared to Chloroquine (5.47μM)[8] thus implying that HCQ has the potential to be used in the management of COVID-19.

In another study on 62 patients using randomized clinical technique, it was found that the group who received standard treatment with an additional 5 days of hydroxychloroquine compared to standard treatment alone experienced a reduction in the symptoms of pneumonia [9]. This suggests that HCQ has the capability to manage the symptoms of SARS-CoV-2. However, there are several adverse effect such as arrhythmia, prolongation of QT interval,[5] retinopathy, bone marrow suppression, seizure and hypoglycemia[7] that should be monitored when using this drug.

AZITHROMYCIN

Azithromycin, a macrolide antibiotic, has also shown to be efficacious in the management of COVID-19. [6] In France, a non-randomized study on 36 patients was done to compare the outcome between patients who receive hydroxychloroquine alone compared to hydroxychloroquine combined with azithromycin. Results showed that in 6

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days there was no viral load detected on nasopharyngeal swab of all the patients who received combination therapy compared to approximately half of patients who received hydroxychloroquine alone (P<0.001)[10]. This suggests that Azithromycin act synergistically with Hydroxychloroquine and increase the effectiveness of the drug as a therapy of COVID-19.

FAVIPIRAVIR

Favipiravir known to have an ability to treat SARS CoV-2 as it inhibit RdRp of RNA viruses [10] . Several studies were conducted to demonstrate the effectiveness of the drug to be used in the management of COVID-19. A study on 240 patients with COVID-19 using randomized clinical technique was divided into Favipiravir and Arbidol classes, equally. The Favipiravir group received 1600 mg twice daily and 600 mg twice for another 9 days orally and the other group received 200mg thrice per day of Arbidol along with conventional therapy. The result shows no significant difference in day 7 clinical recovery time (P= 0.1396), noninvasive mechanical ventilation or auxiliary oxygen therapy (P>0.05) between both drugs but Favipiravir reduced the duration of cough and pyrexia with a difference of 1.75 days and 1.70 days respectively (P<0.0001). There was also an increase in serum uric acid in 16 patients who used Favipiravir (p=0.0014) which demonstrated the adverse effect of this drug. [11] This indicated that Favipiravir has capability in reducing the symptoms of COVID-19 and has mild side effect.

Another study was conducted for 14-day on 35 patients in Favipiravir group and received oral Favipiravir with aerosol inhalation of 5000000 IU interferon (IFN)-α whereas 45 patients in the control group received Lopinavir/Ritonavir (100 mg/ 400mg two times daily) with IFN-α via aerosol inhalation. The result concluded that Favipiravir group demonstrated shorter time of viral clearance compared to the control group, 4 and 11 days respectively, P<0.001. Other than that, improvement in CT chest was also found in Favipiravir group (91.43%) compared with control group (62.22%) (P=0.004)[12]. Therefore, Favipiravir was proven to be highly effective than Lopinavir/Ritonavir as a treatment for COVID-19.

Due to the side effects associated with conventional therapy, it is important to also explore the potential of alternative methods of treatment being used either in replacement or in combination with the current conventional drugs available. Some of these methods, such as honeybee products, Chinese herbal therapy, Nigella sativa and curcumin have been beneficial in the treatment of various other diseases and so, could also prove to be of value in treating COVID-19.

Honeybee products

Honeybee products such as honey, propolis, bee pollen, bee venom and royal jelly exhibit antiviral properties due to their osmotic effect, low pH, and mainly due to certain phytochemical compounds .[16] Honeybee products also stimulate the immune system and this was shown in an animal study done using 256 quail chicks. The addition of honey, propolis, bee pollen and royal jelly to the diet for 42 days resulted in significantly higher antibody titres against the influenza virus (H9N2) ($p< 0.01$).[17] Besides the influenza virus, honeybee products have also shown positive results against herpes simplex virus in an animal study done for 6 days using herpes simplex virus type 1 infected mice. Brazilian propolis markedly reduced virus levels without toxicity and also showed immunological activity. [18] However, there is a lack of data available on the effect of honeybee products on human coronaviruses. This highlights that more research needs to be done as the infection pathways of SARS-CoV-2 could potentially be inhibited via similar mechanisms. [19]

An in- silico study was done whereby 6 honeybee and propolis compounds were found to potentially act against the SARS-CoV-2 main protease (Mpro). [20] The phytochemicals quercetin and kaempferol found in bee pollen have also demonstrated anti-oxidative activity which could be crucial in preventing immunologic complications potentially leading to ARDS, which is one of the major causes of death in covid-19 patients. [21] Royal jelly is another honeybee product which has strong antibacterial and antifungal properties making it useful in preventing opportunistic infections among COVID-19 patients. [22] Bee venom, despite its danger in high concentrations, has been found to be useful in low concentrations up to 5 µg/mL. In a study done, the co-incubation of non-cytotoxic concentrations of bee venom with herpes simplex viral suspension was found to produce a 9-fold reduction in the virus titre ($p < 0.05$). [23]

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Traditional Chinese Herbal Therapy

Another consideration is Traditional Chinese herbal therapy which is the prescription of a Chinese herb mixture based on Chinese diagnostic methodologies of the patient's symptoms. Chinese herbs have been beneficial in past similar epidemics such as SARS-CoV and influenza A H1N1 due to their antiviral properties. [24] A combined formula of YuPingFeng powder and SangJu decoction was found to have immunomodulatory effects that prevented SARS-CoV in a controlled study done by Lau et al. None of the 1063 hospital care workers who took the modified formula contracted SARS, while 0.4% in the control group contracted SARS (P=0.035).[25,26] This evidence highlights the potential of Chinese herbs in treating COVID-19 due to the many similarities between SARS-CoV and SARS-CoV-2. [27] Several studies have been done to evaluate the efficacy of Chinese herbal formula in treating COVID-19 patients. A molecular docking study was done to identify the herb-derived constituents that could interact with human ACE2, the host cell receptor for SARS-CoV-2. 5 compounds, including Scutellarin, Baicalin, Glycyrrhizin, Nicotianamine and Hesperetin were identified with the potential to treat COVID-19. [28] A clinical trial was also done using Qing FeiPai Du decoction given to 214 COVID-19 patients for 3 days. This resulted in a total effective rate above 90% with a 60% improvement in symptoms and imaging performance of patients. Symptoms in 30% of patients stabilised and 130 patients were completely cured. [29]

Nigella Sativa

Another potential herb that can be considered is Nigella sativa (N.sativa) commonly known as black cumin mainly found in the Middle East, Europe, and Asia. Nigella sativa seeds contain various ingredients such as moisture, oil, proteins, carbohydrates, vitamins and mineral. A more important component to note is thymoquinone, a part of volatile oil and an active compound found in black cumin, has been found to be responsible for most of the pharmacological effects. (4) A HIV-positive adult was treated with N.sativa, 10ml twice daily and resulted in a seronegative Western Blot Assay after 6 months. (5) Additionally, HCV positive Egyptian patients were found to have decreased viral load and oxidative stress after consuming N.sativa on regular basis for almost 3 months in a clinical trial.(4) These outcomes along with others studies suggested that N.sativa is a potent anti-viral drug thus, resulting in a molecular study being conducted to explore its pharmacological effects.

Dithymoquinone (DTQ), thymoquinone (TQ) and few other effective compounds found in N. Sativa were tested using a molecular study for their therapeutic effects. Dithymoquinone (DTQ), a carbonal polymer of thymoquinone had the highest binding affinity (8.6kcal/mol) towards the ACE receptor interface (5). It then acts as a competitive inhibitor through its binding. This is important because the receptor acts as the key ingredient in the pathogenesis of covid-19. The spike protein found in SARS-CoV-2 attaches itself to the ACE2 receptor therefore allowing the entry of the virus into the host (6). Nigella Sativa exhibits a stronger binding affinity towards ACE receptor compared to chloroquine and hydroxychloroquine with values of 7.1 kcal/mol and 6.8kcal/mol respectively. This makes it a more suitable drug to be used in the management of covid-19. (7)

Pharmacologically, one or more parts of N.Sativa seeds possesses the ability to reduce toxicity due to its anti-oxidant activities. A study has demonstrated a significant decrease in plasma malondialdehyde (MDA) levels with rise in activity of in erythrocyte glutathione peroxidase (GSH-Px) and superoxide dismutase in 30 post-menopausal women after 2 months of consumption of Allium sativum and Nigella Sativum indicated that it has a role as an anti-oxidant. (4)

Nigella sativa does not only have anti-oxidant properties but is also an anti-inflammatory. Another study N. Sativa proved to play a role as an anti-inflammatory agent as 40 female patients with Rheumatoid Arthritis showed significant improvement in their symptoms after consuming N.sativa oil capsules(500mg) twice daily compared to the placebo ($P<0.05$). (4)

Curcumin

Curcumin is an important bioactive component of turmeric power, derived from Curcuma longa, a rhizome plant. Curcumin is composed of three major components, commonly referred to as the curcuminoids which are curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Being a widely available broad spectrum anti-viral drug against other RNA viruses, curcumin has a potential to be used in treating covid-19 due to its pharmacological effects and is proven by several studies. (1)Curcumin was found to inhibit the main M^{Pro} protease of SARS-CoV-2 thus blocking the replication of the virus by binding to it. It exerted higher binding affinity than hydroxychloroquine (7.75kcal/mol) towards M^{Pro} protease suggesting it a potent anti-viral candidate in managing Covid-19 patients..(2) Moreover, a cell study showed that curcumin blocked the duplication of the SARS-CoV by inhibiting the 3Cl protease.(1) This suggests that curcumin may have antiviral properties useful in the treatment of COVID-1. It is also interesting to note that curcumin is a natural product and studies have yet to reveal any significant toxicity associated with the compound.

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Other additional studies proved that curcumin decreases the circulating cytokines by inhibiting NF-kB pathway, a signalling pathway responsible in development of respiratory distress in SARS-CoV-2 infection in our body(1). It demonstrated that curcumin down regulates IL-6 and TNF-alpha levels according to two meta-analyses of randomized controlled trials thus, preventing the exacerbation of inflammatory reaction in Covid-19 patients.(1) It has demonstrated that curcumin lowers the circulating IL-6 compared to baseline IL-6 concentration (p=0.005).(3) Having anti-oxidant properties, curcumin also reduces the mortality and morbidity in severe covid-19 patients. It was found that in a study with a ventilator-induced lung injury mice, curcumin decreased the malondialdehyde (MDA) level and improved the amount of xanthine oxidase (XO) and total anti-oxidative capacity (TAOC).(1)
Additional studies also revealed curcumin also has other effects which includes of anti-pyretic, anti-emetics, anti-fatigue and bronchodilator effects which makes all in one candidate for covid-19.(1) For example, curcumin has shown to reduce fever and improve physical function in an animal study. (1)Furthermore, administration of curcumin in a mouse model of asthma for 15 minutes has shown a decrease in bronchoconstriction suggesting curcumin can treat respiratory symptoms associated with Covid-19(1). This concludes that curcumin as a whole can improve the signs and symptoms of the Covid-19 patients.

Combination of Conventional and Alternative Therapies

Compared with the single agent treatment of COVID-19 using conventional therapy, the combination of alternative therapies with standard drugs may have better effects on treatment outcomes. From a meta-analysis done of 90 peer-reviewed articles, it was suggested that the addition of alternative therapies resulted in quicker symptom improvement, shorter hospital stay, shorter duration and dosage of treatment as well as a reduced risk of adverse effects and complications. [37,38]
These benefits were further highlighted in a study involving 200 COVID-19 patients, where half of the patients (control group) were treated with Arbidol hydrochloride while the other half (trial group) were treated with Arbidol hydrochloride combined with ShufengJiedu for 14 days. On the 5th day of treatment, results showed that the inflammatory marker levels were significantly lower in the trial group ($P < 0.05$) whereas the abatement of fever, leucocyte count as well as the resolution of chest CT findings were significantly higher in the trial group ($P < 0.05$). The recovery rate was also significantly lower (80%) in the control group with ($P < 0.05$). This suggests that the combination of Arbidol and ShufengJiedu for COVID-19 treatment would be highly effective. [39]
The efficacy of curcumin combined with conventional drugs was also tested. 8 new conjugate drugs were designed by combining curcumin and hydroxychloroquine. The potential of these new co-drugs to better inhibit the SARS-CoV-2 virus was then tested via molecular docking. The docking results revealed that the 8 co-drug molecules had promising binding affinity against the COVID-19 main protease (Mpro) and Interleukin-1B compared to the standard drugs. This synergistic mode of action suggests that they could be highly effective against COVID-19. [40]
We would like to propose a combination of QingFeiPaiDu and Arbidol hydrochloride due to their potent inhibitory action on SARS-CoV-2 entry by binding to the ACE2 receptor. Furthermore, they also have anti-inflammatory and immunoregulatory properties. We also suggest a combination of Nigella Sativa and hydroxychloroquine as they also share the action of binding to the ACE2 receptor which can produce a synergistic effect to inhibit the entry of the virus into the host body. Another combination is Favipiravir and curcumin, which both exhibit antiviral effect by inhibiting RNA polymerase and protease respectively. So, their synergistic interaction would have the potential to produce better antiviral effects on the virus.

CONCLUSION

This paper proposes that the combination of conventional and alternative therapy is a more suitable option for managing covid-19 patients. We hypothesize that adding alternative therapy to conventional therapy will bring more benefits than conventional therapy alone as seen from the many clinical trials conducted. Patients treated with combination therapy experienced significant improvement in multiple aspects compared to those who were only treated with the standard drugs. However, more clinical trials are needed to properly establish the role and benefits of alternative therapies in managing the patients of COVID-19. This is because there are limitations in the understanding of side effects, cost, availability and the applicability of alternative medication to the wider general population.

LIMITATIONS

We acknowledge limited access to some of the articles in the search engine is part of the limitation of this review.

CONFLICTING INTEREST

The authors declare that they have no conflicting interest.

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