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Minireview

Phytochemicals against COVID-19 and a gap in clinical investigations: An outlook

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The novel coronavirus 2019 (COVID-19) has presented an unexpected pandemic that has triggered severe panic among people worldwide. In this direction, nations are maximizing their efforts to battle the disease and lower illness. Plants that produce numerous bioactive compounds might help develop and keep immunity against chronic diseases and COVID-19. Medicinal plant-based treatments are trendy in rural and tribal communities, mainly as an outcome of the increased scalability, which causes them to be cheaper and affordable compared to present-day medication. Furthermore, additional research on the antiviral possibility of healing plants shown that plant extracts with incredibly energetic secondary metabolites are competent to interrupt the replication of numerous very pathogenic viruses. But the testing and clinical trials take a very long time. This review discusses the gap in clinical studies with available phytochemicals and the possible ways to cover the same.

Keywords: COVID-19, Pandemic, Phytochemicals, Trials

Present unprecedented coronavirus pandemic declared by the World Health Organization (WHO) is liable for exponential development of healthcare interest in coronaviruses globally[1]. Coronaviruses (CoVs) are a member of the family Coronaviridae and can infect both humans and animals[2]. Based on their serological and genotypic characteristics, the α-coronaviruses and β-coronaviruses genera of Coronaviridae family have practically every coronavirus which can infect humans[3]. The observed symptoms in infected individuals were fever, pulmonary infiltration, hypoxemia, thrombocytopenia, lymphopenia, leucopenia, dyspnea, diarrhoea, myalgia, headache, cough, and disturbed renal and hepatic function resulting in death in certain individuals[4]. Nevertheless, there exists no remedy, drug, or perhaps vaccine for the healing of COVID-19[5].

Naturally occurring phytochemicals offer a powerful and valuable aid of chemical elements displaying antiviral properties. Additional chemical modification of these components, guided by computer-based docking simulations, may additionally boost their potency or selectivity[6,7]. Several of the important phytochemicals that show promise for the healing of coronavirus in people consist of, polyphenols, lectin, silvestrol, and psoralidin[8]. Needless to point out, these compounds might be harmful at specific levels, and thus *in vitro* and *in vivo* testing is necessary to choose therapeutic and safe classes for every combination before medical trials in people are performed[9]. Initial studies might concentrate on compounds that have been accredited for medication consumption in the past and are viewed as protected by national organizations and the situation for several polyphenolic compounds[10]. It ishopeful that researchers are instructed by this info offered here to build safe, effective anti-coronavirus healing agents from obviously derived ingredients.

Furthermore, standard herbal medicines and purified items that are organic might steer the enhancement of novel antiviral drugs[11]. Additionally, in the current outbreak of COVID-19, a lot of people appear to be looking at complementary or perhaps even traditional healing treatments, albeit using them pretty much entirely together with western medicine[12,13]. Nevertheless, dependent on the substantial scientific tests done on this specific topic, it is hard to sort the probable effects of, and interaction between, traditional natural medicine and western medicine[14]. In this direction, several studies have highlighted the role of traditional Chinese medications as a potential cure against COVID-19[15]. Broad-spectrum of the activities of phytochemicals can have multiple healing potentials. It is hoped the information given might guide the derived drug discovery process in finding a cure for

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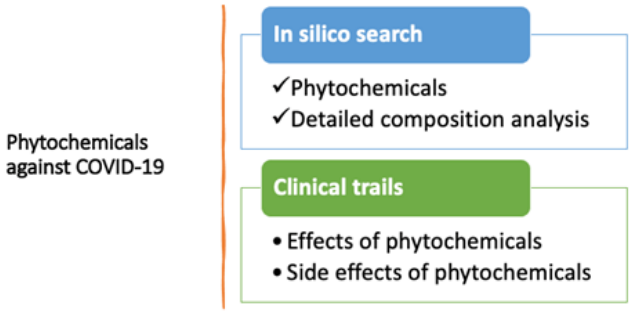

Fig. 1 — A summary of the methodology used to identify the most effective phytochemicals against COVID-19

COVID-19[16]. Molecular docking with molecular dynamics simulation is commonly applied to screen prospective drug candidates against COVID-19. Literature is full of reports on the efficacy of phytochemicals against COVID-19. Consequently, with the claim that these compounds are possible anti-COVID drugs; thus, the researcher within this area must confirm the working with *in vitro* experimental methods and further confirmation with the large-scale clinical trials[17-21]. This review highlights the gaps in clinical studies with phytochemicals as well as the possible ways to go over the same (Fig. 1).

Gaps in Clinical Studies

A comparative analysis was performed to compute the program amount of countless experimental medicines recognized in China, determined by the present treatment techniques, together with talking about recently published literature on COVID-19 pandemic[22]. Nevertheless, it has been discovered that several plant species are used for a substantial amount of time in dealing with infectious diseases. In this direction, two regular Chinese natural medicines' Sang Ju Yin' and' Yu Ping Feng San' were utilized to observe the modifications of the defense system in total variety cellular, and the realization demonstrated that it might alter T cells that help boost up the vast variety safeguard capacity[23,24]. Furthermore, these excellent traditional Chinese medicine outcomes under controlled healthcare trials were also supported by lab primarily based *in vitro* study[25,26]. On yet another hand, additional scientific tests must shed light on the devices and pathways targeted by such things, which will help to improve their medical usefulness.

Moreover, detailed studies are needed to prove the benefits of medicinal compounds because of the absence of clinical trials (or maybe minimal evidence) or perhaps because of research not necessarily introduced to COVID-19 patients[27,28]. This astonishing discrepancy between phytochemicals reported by researchers as a potential cure of COVID-19, as well as the apparent lack of readily available information in the form of national recommendations, is astonishing, and this is preventing the large-scale utilization of plant-based cures[12]. In this direction, a survey of the ClinicalTrials.gov trial registry database showed that there are in total 9 trials at the different phase and only one is completed with the use of Brazilian green propolis rest all are in the recruiting, not yet recruiting and enrolling stage (Table 1). Furthermore, there were 1,258 studies with the use of plant-based cure in the entire database, and only 9 were under evaluation for the COVID-19. Overall, there were 3,849 studies undergoing trials for the COVID-19 as of November 2020. Whereas, based on the survey of Chinese clinical trial registry database (http://www.chictr.org.cn/index.aspx) showed only 3 studies using the plant-based cure for COVID-19 (Table 2). This disparity between them against treating organic cures as the red-headed stepchild of supporting cancer care as well as for (re)assessing which plants-based treatment will be advised based on their backing by large scale clinical trials.

Sealing the Gap

Trial methods may be substantially improved to increase the medical value and common comfort of trial results, by incorporating subjects from usually underrepresented sociodemographic groups as well as employing more naturalistic techniques considerably to treatment, performing more comparison trials as compared to most acceptable available approaches, growing the uses of trials to contend with interventions beyond chemotherapeutics, along with improving methods for looking at the long-term effects of treatment[29,30]. The problem of generalizability is frequently viewed as the primary limitation of randomized trials[31]. Therefore, the trial results may vary significantly less applicable to many treatment choices, though the people there have the same signs and symptoms[32]. Also, consider whether a person has comorbid situations or perhaps an increased risk of bad outcomes attributable to things beyond the natural characteristics of the state, which will influence the possible risks and benefits of treatment[33].

One specific area where there might be enhancement is in a broader representation of people from different racial and cultural organizations[34]. The generalizability of trial advantages would similarly be enhanced by participation in a far better quantity of

Table 1 — List of plant-based studies identified from a survey of the ClinicalTrials.gov trial registry database as of December 2020

Sl. No	Status	Study Title	Conditions	Interventions
1	Recruiting	Randomized Proof-of-Concept Trial to Evaluate the Safety and Explore the Effectiveness of a Plant Polyphenol for COVID-19	COVID-19	Drug: Plant Polyphenol Dietary Supplement: Vitamin D3
2	Enrolling by invitation	Phytomedicines Versus Hydroxychloroquine as an Add on Therapy to Azythromycin in Asymptomatic COVID-19 Patients	COVID-19	Combination Product: Hydroxychloroquine/Azithromycine Combination Product: Quinquina-Stevia/Azythromycin Combination Product: 4Plants/Azythromycin
3	Completed	The Use of Brazilian Green Propolis Extract (EPP-AF) in Patients Affected by COVID-19	COVID-19	Drug: Brazilian Green Propolis Extract (EPP-AF) Other: Standard care
4	Not yet recruiting	COVID-19: Collecting Measurements of Renin-angiotensin-system Markers, Such as Angiotensin-2 and Angiotensin 1-7	COVID-19	Combination Product: Tomeka® Drug: "Vernonia amygdalina"
5	Recruiting	The Effect of Aromatherapy on COVID-19-induced Anxiety	Stress COVID-19 Anxiety	Other: Essential Oil Blend Other: Control Blend
6	Recruiting	Describing Chinese Herbal Medicine Telehealth Care for Symptoms Related to Infectious Diseases Such as COVID-19	Coronavirus Infection	Dietary Supplement: Chinese Herbal Medicine
7	Not yet recruiting	CBD Oil for Reducing Emotional Impact of COVID-19	Anxiety Depression Alcohol Abuse Substance Abuse	Dietary Supplement: CBD Isolate Dietary Supplement: Full Spectrum CBD Oil Dietary Supplement: Placebo Oil
8	Not yet recruiting	Effect of a Nss to Reduce Complications in Patients With COVID-19 and Comorbidities in Stage III	COVID-19 Diabetes Mellitus Hypertension Obesity	Dietary Supplement: Nutritional support system (NSS) Other: Control
9	Recruiting	Outcomes Mandate National Integration With Cannabis as Medicine for Prevention and Treatment of COVID-19	COVID-19 Chronic Pain Chronic Pain Syndrome Chronic Pain Due to Injury	Drug: Cannabis, Medical

Table 2 — List of plant-based studies identified from a survey of Chinese clinical trial registry database (http://www.chictr.org.cn/index.aspx) as of December 2020

Registration number	Public title	Type	Registration Date
ChiCTR2000030503	Extracorporeal blood purification therapy using Li's Artifical Liver System for patients with severe novel coronavirus pneumonia (COVID-19) patient	Interventional	2020/03/05
ChiCTR2000030223	Quality of life among Chinese residents during and after novel coronavirus pneumonia (COVID-19) outbreak: an online survey	-	2020/02/26
ChiCTR2000030215	Study for the efficacy of Kangguan No. 1-3 prescription in the treatment of novel coronavirus pneumonia (COVID-19)	Interventional	2020/02/25

coaching sorts among recruiting facilities for medical trials[35]. Nevertheless, medical studies of far more prevalent problems would acquire from that diversification. A variety of novel trial styles happen to be suggested to handle this problem and additionally to enhance the participation of subjects who might not ordinarily get engaged in a clinical trial since they are uncomfortable with the idea of remaining randomly given to treatment[36]. The utilization related to a second "rescue" medicine in case an issue does not react to the initial therapy is going to be an example associated with a fixed adaptive design. A mostly randomized affected individual preference layout trial is similar in that subjects could select the treatment of theirs[37]. In an attempt on the invention, the possibility of choosing a

chosen therapy or perhaps which makes it easy for themselves to be randomized. The big, simple trial paradigm is a substitute for these novel versions[38]. The gains associated with an extensive, simple trial will be its inclusiveness, value to the usual workout atmosphere, and a naturalistic approach to therapy.

Conclusion

Naturally occurring phytochemicals provide a valuable and powerful aid of synthetic parts displaying antiviral properties. It is hoped that this information instructs researchers offered right here in the technique of creating safe, highly productive anti coronavirus healing parts from naturally derived ingredients. Instead, our goal is usually to collate information over the wonderful spectrum of excellent phytochemicals from a selection of plant species that might have healing potential. A great deal of novel trial kinds happens to be backed by handling this material and to improve the participation of subjects which would more than likely not ordinarily get interested in a clinical trial since they're uncomfortable with the idea of trying to keep arbitrarily provided to therapy. The utilization associated with a second "rescue" medicines in case an issue doesn't react to the initial treatment is going to be a great case related to a fixed adaptive style. A usually randomized affected personal preference layout trial is reasonably similar in that subjects might choose their healing of theirs. Phytochemicals are readily available near households and are widely domesticated throughout even in the world's semi-arid and dry regions. Due to numerous bioactive compounds in their leaves, fruit, *etc*., including vitamins, polyphenols, and amino acids. It is only because of the critical need for therapeutic interventions for COVID-19, caused by the SARS-Coronavirus, that so much attention is needed right now to repurposed not only antiviral drugs but also to natural products and herbal medications. Alternatively, it may serve as a springboard for future clinical trials examining the efficacy of several commercially available phytochemical supplements in improving the health status of COVID-19 patients, as well as for experimental studies characterizing the aforementioned ligand–protease interaction.

Furthermore, extra exploration on the antiviral chance of healing plant life disclosed that plant extracts with extremely lively secondary metabolites are adept at disrupting the replication of many extremely pathogenic viruses. Nevertheless, clinical trials and testing may have genuine time. Moreover, for dealing with the issues like biopiracy, the nation ought to bioprospecting its ethnomedicinal understanding wherein local communities and indigenous people must be the primary element. Their knowledge and voices must be mirrored in the decision-making procedures. Traditional medication-based bioprospecting would supply unmatched eco-friendly chemical substances and their promising brand-new leads. It is time to be vocal about local items and helps these hometown items to be global. Cross-cultural knowledge of medicinal plants and their therapeutic uses could further intensify the development of more affordable, effective, and safer medicines against COVID-19. To be able to commercialize novel formulations at a worldwide level, the nation must be vocal towards traditional knowledge.

Conflicts of interest

All authors declare no conflicts of interest.

References

1 Chitra J, Rajendran SM, Jeba JM & Jeyakanthan J, Impact of COVID-19 lockdown in Tamil Nadu: Benefits and challenges on environment perspective. *Indian J Biochem Biophys*, 57 (2020) 370.

2 Seah I & Agrawal R, Can the coronavirus disease 2019 (COVID-19) affect the eyes? A review of coronaviruses and ocular implications in humans and animals. *Ocul Immunol Inflamm*, 28 (2020) 391.

3 Joseph AA & Fagbami AH, Coronaviruses: a review of their properties and diversity. *Afr J Clin Exp Microbiol*, 21 (2020) 258.

4 Lima CMA de O, Information about the new coronavirus disease (COVID-19). *Radiol Bras*, 53 (2020) V.

5 Robson B, COVID-19 Coronavirus spike protein analysis for synthetic vaccines, a peptidomimetic antagonist, and therapeutic drugs, and analysis of a proposed achilles' heel conserved region to minimize probability of escape mutations and drug resistance. *Comput Biol Med*, 121 (2020) 103749.

6 Alamri MA, Altharawi A, Alabbas AB, Alossaimi MA & Alqahtani SM, Structure-based virtual screening and molecular dynamics of phytochemicals derived from Saudi medicinal plants to identify potential COVID-19 therapeutics. *Arab J Chem*, 13 (2020) 7224.

7 Islam R, Md. Parves R, Paul AS, Uddin N, Md. Rahman S, Al Mamun A, Md. Hossain N, Md. Ali A & Md. Halim A, A molecular modeling approach to identify effective antiviral phytochemicals against the main protease of SARS-CoV-2. *J Biomol Struct Dyn*, 9 (2020) 1.

8 Sharma V, Saini I, Yadav VK, Jayaswal D, Singh G, Kesh H, Srivastava A & Kaushik P, Impact of COVID-19 pandemic on vegetable sector and its allies. *Indian J Tradit Know*, 19 (2020) 177.

9 Marx U, Andersson TB, Bahinski A, Beilmann M, Beken S, Cassee FR, Cirit M, Daneshian M, Fitzpatrick S, Frey O, Gaertner C, Giese C, Griffith L, Hartung T, Heringa MB, Hoeng J, de Jong WH, Kojima H, Kuehnl J, Luch A, Maschmeyer I, Sakharov D, Sips AJAM, Steger-Hartmann T, Tagle DA, Tonevitsky A, Tralau T, Tsyb S, van de Stolpe A, Vandebriel R, Vulto P, Wang J, Wiest J, Rodenburg M &

Roth A, Biology-inspired microphysiological system approaches to solve the prediction dilemma of substance testing. *Altex*, 33 (2016) 272.

10 Quideau S, Deffieux D, Douat-Casassus C & Pouysegu L, Plant polyphenols: chemical properties, biological activities, and synthesis. *Angew Chem Int Ed Engl*, 50 (2011) 586.

11 Mukherjee PK, *Quality Control and Evaluation of Herbal Drugs: Evaluating Natural Products and Traditional Medicine*. (Elsevier) 2019, 56.

12 Jahan I & Ahmet O, Potentials of plant-based substance to inhabit and probable cure for the COVID-19, *Turk J Biol*, 44 (2020) 228.

13 Hang J, Xie B & Hashimoto K, Current status of potential therapeutic candidates for the COVID-19 crisis. *Brain Behav Immun*, 87 (2020) 59.

14 Pound P, Britten N, Morgan M, Yardley L, Pope C, Daker-White G & Campbell R, Resisting medicines: a synthesis of qualitative studies of medicine taking. *Soc Sci Med*, 61 (2005) 133.

15 Kumar NRP & Shetty N, Machine learning approach for COVID-19 crisis using the clinical data. *Indian J Biochem Biophys*, 57 (2020) 602.

16 Mukhtar M, Arshad M, Ahmad M, Pomerantz RJ, Wigdahl B & Parveen Z, Antiviral potentials of medicinal plants. *Virus Res*, 131 (2008) 111.

17 Prasanth DSNBK, Murahari M, Chandramohan V, Panda SP, Atmakuri LR & Guntupalli C, *In silico* identification of potential inhibitors from Cinnamon against main protease and spike glycoprotein of SARS CoV-2. *J Biomol Struct Dyn*, (2020) 1.

18 Chaudhary S, Rai P, Sesham K, Kumar S, Singh P, Nag TC, Chaudhuri P, Trikha A & Yadav SC, Microscopic imaging of bronchoalveolar fluids of COVID-19 positive intubated patients reveals the different level of SARS-CoV-2 infection on oral squamosal epithelial cells. *Indian J Biochem Biophys*, 58 (2021) 196.

19 Lokhande KB, Doiphode S, Vyas R & Swamy KV, Molecular docking and simulation studies on SARS-CoV-2 Mpro reveals Mitoxantrone, Leucovorin, Birinapant, and Dynasore as potent drugs against COVID-19. *J Biomol Struct Dyn*, 20 (2020) 1.

20 Pandey P, Rane JS, Chatterjee A, Kumar A, Khan R, Prakash A & Ray S, Targeting SARS-CoV-2 spike proteinof COVID-19 with naturally occurring phytochemicals: an *in silico* study for drug development. *J Biomol Struct Dyn*, 38 (2020) 1.

21 Rahman MM, Saha T, Islam KJ, Suman RH, Biswas S, Rahat EU, Md. Hossen R, Islam R, Md. Hossain N, Al Mamun A, Khan M, Md. Ali A & Md. Halim A, Virtual screening, molecular dynamics and structure–activity relationship studies to identify potent approved drugs for COVID-19 treatment. *J Biomol Struct Dyn*, 7 (2020) 1.

22 Ghosh S, Dey S & Ghosh S, Diabetes in the time of COVID-19 pandemic: A knife with two sharp ends. *Indian J Biochem Biophys*, 57 (2020) 512.

23 Ren JL, Zhang AH, & Wang XJ, Traditional Chinese medicine for COVID-19 treatment. *Pharmacol Res*, 155 (2020) 104743.

24 Mirzaie A, Halaji M, Dehkordi FS, Ranjbar R & Noorbazargan H, A narrative literature review on traditional medicine options for treatment of corona virus disease 2019 (COVID-19). *Complement Ther Clin Pract*, 40 (2020) 101214.

25 Fung FY & Linn YC, Developing traditional Chinese medicine in the era of evidence-based medicine: current evidences and challenges. *Evid Based Complement Alternat Med*, 4 (2015) 425037.

26 Yang Y, Islam MS, Wang J, Li Y & Chen X, Traditional Chinese medicine in the treatment of patients infected with 2019-new coronavirus (SARS-CoV-2): a review and perspective. *Int J Biol Sci*, 16 (2020) 1708.

27 Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, Oczkowski S, Levy MM, Derde L, Dzierba A, Du B, Aboodi M, Wunsch H, Cecconi M, Koh Y, Chertow DS, Maitland K, Alshamsi F, Belley-Cote E, Greco M, Laundy M, Morgan JS, Kesecioglu J, McGeer A, Mermel L, Mammen MJ, Alexander PE, Arrington A, Centofanti JE, Citerio G, Baw B, Memish ZA, Hammond N, Hayden FG, Evans L & Rhodes A, Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med*, 46 (2020) 854.

28 Picot S, Marty A, Bienvenu AL, Blumberg LH, Dupouy-Camet J, Carnevale P, Kano S, Jones MK, Daniel-Ribeiro CT & Mas-Coma S, Coalition: Advocacy for prospective clinical trials to test the post-exposure potential of hydroxychloroquine against COVID-19. *One Health (Elsevier)*, 9 (2020) 1.

29 Curry LA, Nembhard IM & Bradley EH, Qualitative and mixed methods provide unique contributions to outcomes research. *Circulation*, 119 (2009) 1442.

30 Yadav VK, Singh G, Jha RK, & Kaushik P, Visiting Bael (*Aegle marmelos*) as a protective agent against COVID-19: A review. *Indian J Tradit Know*, 19 (2020) 153.

31 Rothwell PM, External validity of randomised controlled trials: "to whom do the results of this trial apply?". *Lancet*, 365 (2005) 82.

32 Ansarin K, Tolouian R, Ardalan M, Taghizadieh A, Varshochi M, Teimouri S, Vaezi T, Valizadeh H, Saleh P, Safiri S & Chapman KR, Effect of bromhexine on clinical outcomes and mortality in COVID-19 patients: A randomized clinical trial. *BioImpacts*, 10 (2020) 209.

33 Shah S, Diwan S, Soin A, Rajput K, Mahajan A, Manchikanti L, Kaye AD, Hirsch JA & Gharibo C, Evidence-Based Risk Mitigation and Stratification During COVID-19 for Return to Interventional Pain Practice: American Society of Interventional Pain Physicians (ASIPP) Guidelines. *Pain Physician*, 23 (2020) S161.

34 Kreuter MW, Lukwago SN, Bucholtz DC, Clark EM & Sanders-Thompson V, Achieving cultural appropriateness in health promotion programs: targeted and tailored approaches. *Health Educ Behav*, 30 (2003) 133.

35 Voss R, Gardner R, Baier R, Butterfield K, Lehrman S & Gravenstein S, The care transitions intervention: translating from efficacy to effectiveness. *Arch Intern Med*, 171 (2011) 1232.

36 Chen X, Zhu R, Jin Y, Liu J & Sun C, Investigation and analysis of the mental pressure of outpatient medical attendants and nurses during the COVID-19 pandemic in china. *Indian J Biochem Biophys*, 58 (2021) 261.

37 Hörnberg H, Pérez-Garci E, Schreiner D, Hatstatt-Burklé L, Magara F, Baudouin S, Matter A, Nacro K, Pecho-Vrieseling E & Scheiffele P, Rescue of oxytocin response and social behaviour in a mouse model of autism. *Nature*, 584 (2020) 252.

38 Charles H. Evans J & Ildstad ST, *Design of Small Clinical Trials*. (National Academies Press (US)) 2001, 121.