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Research Article

CLINICAL RESEARCH OF NATURAL PLANTS FOR THE TREATMENT OF CORONAVIRUS: A BIBLIOMETRIC ANALYSIS AND FUTURE RESEARCH PLAN

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Abstract

The COVID-19 virus has resulted in numerous deaths. The situation is exacerbated because many people with preexisting health conditions and weakened immune systems are not adequately protected by available medications, leading to more fatalities.COVID-19 infects the lungs, causing inflammation and damage that can lead to symptoms like cough and shortness of breath. Severe cases may result in pneumonia or respiratory distress, and some individuals may face long-term lung issues. This kind of hit-and-run virus killer has no vaccine to prevent or protect the body from death and therefore triggers lots of local trials across the globe. This study explores successful local medicinal plants and substances in Africa that have not undergone modern pharmaceutical and clinical trials that produce a vaccine for various viruses. The absence of a specifically certified vaccine hasgiven rise to alternative traditional medicines; however, researchers have been concerned about the dynamics and efficacy of natural medical products since the global lockdown of the pandemic in 2020. Stack evidence from research trials has suggested the potential effectiveness of several natural traditional medicines against the deadly coronaviruses. To this effect, this systematic review explored and summarised representativenatural products for the treatment of coronavirus-related diseases in the past 10 years and demonstrates the prospects of natural products against coronavirus-related diseases by listing herbal plants and natural small molecule compounds and their therapeutic mechanisms,providing references for subsequent related studies.

Keywords: Clinical Research,Natural Plants, Coronavirus, Bibliometric Analysis.

INTRODUCTION

COVID-19 is the disease caused by a coronavirus called SARS-CoV-2. This novel virus was first detected by World Health Organization (WHO) on 31 December 2019, after a cluster of so-called viral pneumonia cases was reported in Wuhan, Republic of China. Since the detection of the COVID-19 virus, the world has been experiencing deaths and an increasing number of those who succumbed to the deadly virus. Existing research has shown that an individual's underlying health and level of immunity are significantly related to the rate of COVID-19 deaths (1). Considering the effect of COVID-19 on elderly people, the United Nations (2020) reported that, the age group between 50-59 had the highest number of COVID-19 deaths regardless of gender. The WHO, in collaboration with nations across the globe, officially declared the novel coronavirus pneumonia caused by COVID-19 a global public health emergency (2). Corona viruses are commonly found in nature. It was first detected in chickens in 1937, and in 1965, British scientists Tyrrell and Almeida et al. This virus was later isolated from the nasal passage of a boy after having a cold (3). Today, several COVID-19 vaccines have been approved by WHO (based on the Emergency Use Authorization Protocol) and by other strict national regulatory agencies for use (4). Significant progress has been made in developing treatments for patients with COVID-19. Anti-COVID-19 therapies for patients should be determined by healthcare workers. This choice depends on the severity of the disease and the risk of its progression, particularly considering the patient's age and any underlying health problems present before the infection (5).

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For treating non-severe COVID-19 cases, several standard medications have been identified and are used to manage symptoms and reduce the risk of progression. For more severe cases, corticosteroids such as dexamethasone have been found to be effective and are commonly administered to help reduce inflammation and improve outcomes (6,7). In addition to these medications, oxygen therapy is a critical and widely used treatment for patients with severe COVID-19, as it helps to ensure adequate oxygen levels in the blood and supports respiratory function. These therapies, when used appropriately, are essential components of the global response to severe COVID-19 cases (8). WHO is leading work to enhance global capabilities and opportunities to make oxygen production, distribution, and supply to patients available (9). Studies suggest that antibiotics do not kill viruses because they only kill bacterial infections (10,11). Knowing that COVID-19 is caused by a virus, antibiotics do not affect it. Antibiotics should not be used as a means of preventing or treating COVID-19 disease. Moreover, doctors in the hospital will sometimes use antibiotics to treat secondary bacterial infections that can be a complication of COVID-19 in severely ill patients (12,13). Hence, antibiotics should only be used as directed by a doctor to treat bacterial infections. However, there have been reported cases of the effective use of natural traditional medicine for the treatment of coronavirus infection, but less attention has been given to this at the global level (14).

LITERATURE REVIEW

COVID-19 Treatment

Treatment strategies for COVID-19 have evolved significantly, addressing varying degrees of illness. For mild cases,

supportive care remains the cornerstone, while more severe cases benefit from antiviral medications, such as remdesivir and molnupiravir, corticosteroids like dexamethasone, and monoclonal antibodies including casirivimab/imdevimab(15). Remdesivir, initially developed for Ebola, accelerates recovery by inhibiting viral replication in hospitalized patients. Favipiravir has demonstrated partial efficacy in symptom management but lacks broad endorsement due to variable results. Molnupiravir introduces errors in the virus's RNA, potentially reducing severe disease risk, and has received emergency use authorization in various regions (12,16). In critically ill patients, dexamethasone plays a crucial role in mitigating inflammation and has been shown to decrease mortality rates. Monoclonal antibodies, such as casirivimab/imdevimab and sotrovimab, neutralize the virus and are most effective when administered early(17). They have been granted emergency use authorization due to their capacity to prevent severe disease progression. Convalescent plasma, derived from recovered individuals, has been employed with inconsistent results. Collectively, these therapeutic approaches, alongside ongoing research, are pivotal in managing COVID-19 and adapting to emerging challenges(18).

Anti-coronavirus effect of natural products

Natural plants have a long history of traditional medicinal use and are known for their diverse array of bioactive compounds. These Natural plants have made a significant contribution to the protection and development of human health (19,20). Preclinical researchers from academic and research institutions have shown serious concern about the efficacy of these inthe treatment of certain ailments and the toxicological assessment of these plants for pharmaceutical purposes(21). While it is important to note that there is currently no specific plant or herbal remedy proven to cure or prevent COVID-19, ongoing research has explored the potential of various African plants in the management and treatment of viral infections, including coronaviruses. These plants are rich in phytochemicals that possess antiviral, immunomodulatory, and anti-inflammatory properties, which may positively impact the symptoms and complications associated with viral infections (22). One notable example is Artemisia annua, commonly known as sweet wormwood or Qinghao. This plant contains a compound called artemisinin, which has been used for decades to treat malaria. Recently, there has been interest in its potential efficacy against COVID-19. While more research is needed, early studies have suggested that artemisinin and its derivatives could inhibit the replication of coronaviruses in vitro (23). African plant of interest is *P. sidoides*, also known as Natural geranium or Umckaloabo. This plant is native to South Africa and has been traditionally used for respiratory infections. Some research has indicated that extracts from *P. sidoides*may possess antiviral activity against respiratory viruses, including coronaviruses. However, further studies are necessary to determine its effectiveness specifically against COVID-19 (24). Similarly, *Hypoxis hemerocallidea* (African potato), has also been traditionally used for its immune-boosting properties and is being investigated for their potential antiviral effects. However, it is important to emphasize that scientific evidence supporting their effectiveness against COVID-19 is still limited (25). It is crucial to note that while these plants may have potential benefits, they should not be considered as standalone treatments for COVID-19. Medical interventions and treatments should always be based on robust scientific evidence and prescribed by healthcare professionals. The World Health Organization (WHO) and other health authorities continue to recommend following official guidelines for the prevention, testing, and treatment of COVID-19 (26).

Antiviral Treatment of COVID-19

Several antiviral treatments have been authorized or approved for the treatment of COVID-19. The landscape of COVID-19 treatments is rapidly evolving, and new information may have emerged since then. According to the World Health Organization (WHO) and the Centres for Disease Control and Prevention (CDC),there are a few antiviral treatments that are being used or studied at present: Firstly, Remdesivir: Remdesivir is an antiviral medication that was initially developed for the treatment of Ebola. It has been authorized for emergency use or approved in some countries for the treatment of hospitalized COVID-19 patients (27). Remdesivir works by interfering with the replication of the virus. It has shown some effectiveness in reducing the duration of hospital stays in severe cases of COVID-19 (28). Secondly, Monoclonal Antibodiesare laboratory-produced proteins that can mimic the body's immune response to a specific virus. Several monoclonal antibody therapies have been authorized or approved for emergency use in high-risk COVID-19 patients. These antibodies are designed to bind to the spike protein of SARS-CoV-2 (the virus that causes COVID-19) and prevent it from infecting human cells (27).Also, Convalescent plasma which is obtained from individuals who have recovered from COVID-19 and contains antibodies against the virus has been used as a treatment option for some hospitalized COVID-19 patients, particularly those with severe disease (29). However, the effectiveness of convalescent plasma is still being studied, and its use may vary depending on local guidelines.Antiviral Research is being investigated in clinical trials for its potential effectiveness against COVID-19. These include drugs like favipiravir and molnupiraviramong others. The efficacy and safety of these drugs are still being evaluated, and it's essential to rely on data from well-conducted clinical trials before concluding their effectiveness. The availability and usage of specific treatments vary depending on the region and local healthcare guidelines (28,30).

METHODOLOGY

Methods Data Sources and search strategy

Articles published from 2008 to 2023 were explored by the author from the PUBMED core collection database for bibliometric analysis. PICO framework study search strategy was employed to address the specific patient's medical needs and intervention techniques (31). Population/problem, to explore the preclinical effective medicinal substances needed for the treatment of coronavirus. I intervention, this study encapsulates various Natural medicinal substances, and plants for treating coronavirus. Comparison, which indicated the difference between the effectiveness of orthodox preclinical trials and Natural medicine. Outcome, which outlined the results of the physiological effects and efficacy of Natural medicine for the treatment of coronavirus. The researcher used the related and specific keywords in Natural medicinal substances, plants, Natural treatment of COVID-19, Natural alternative medicines for COVID-19, and Natural vaccines from studies available in the PUBMED publications. The researcher downloaded related publications for the bibliometric

analysis and extracted the dataset on the publication details such as authors, and titles. This study employed standard weight attributes link and the total link strength attribute of the articles. The weight attributes describe the frequency of links between items and the total strength of the links between the items.

Inclusion and exclusion criteria

The articles for bibliometric analysis were restricted to original articles written in English. The exclusion criteria were as follows: (I) non-English written documents and (II) documents classified as non-original articles.

Data analysis

The study used the intrinsic functions of the *Pubmed*core collection online database to describe the basic features of the detected publications. The study constructs and visualizes co-occurrence networks of co-authorship, co-occurrence, citation, and keyword search using the software of VOS viewer (version 1.6.19; for Microsoft Windows). Keywords that occurred more than five times were defined as high-frequency keywords in the VOS viewer. VOS viewer clustering algorithms were used for the calculation of all the algorithms based on previous guidelines (32).

FINDING

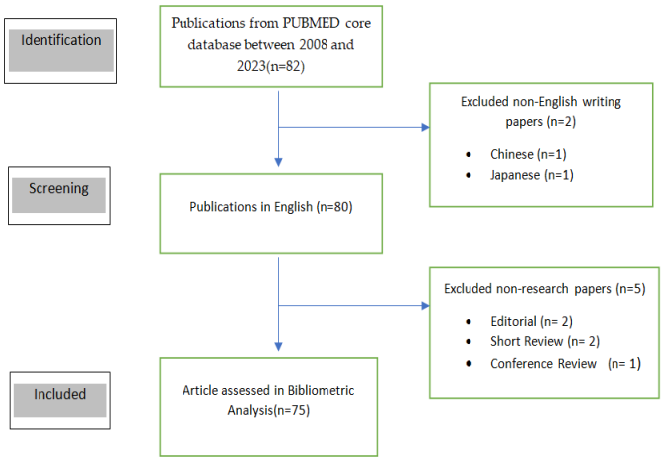
Publications output

Out of the 254 publications, a total of 81 eligible publications were selected for VOS viewer analysis among original articles reviewed, conference papers, book chapters, and other types of articles between 2008 and 2023. It should be noted that almost 99% of the eligible publication's articles were published between 2020 and 2023. Ultimately, 81 English-written research articles were included in the bibliometric analysis (Figure 1).

Growth trend of publications

A sharp significant growth in the number of publications in this field between 2020 and 2023with about 99% of publicationson the effect of COVID-19 in the year 2019 as the trigger for more significant clinical research on Natural plants for the treatment of respiratory illness and boosting of immunity. The total number of articles published before 2020 that met the inclusion criteria was only 1 paper article. This shows the low attention and concerns about Natural medicinal plants and herbal products, especially before the COVID-19 outbreak. The search detected about 74 countries' contributions to the field of artificial intelligence/machine learning in toxicological assessment-related research. The United States of America has the most publications of about (n=249) articles, followed by China (n=127), India (n=93), and the United Kingdom (n=76) respectively. While other countries mostly from Europe and Asia had the remaining publications. Keyword searches identified by the VOS viewer are based on the citation index service of the SCOPUS core collection database. Finally, a total of 1415 keywords were identified from the included articles with 169 meeting the thresholds based on 3 occurrences. Among them, 27 keywords had high frequency and were included in the analysis.

Bibliometric Analysis of Keywords



Co-authorship full counting

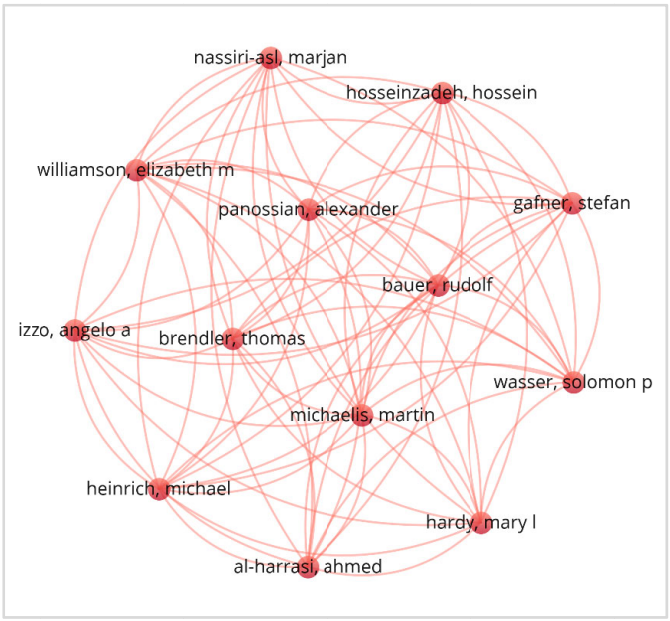


Figure 2.

This search identifies 51 groups of authors with 13 items having the same total link strength of 12. These 13 items of research showa strong level of interconnectivity among preclinical research on Natural plants either through *in vivo* or *invitro* methods of toxicological assessment. This Co-authorship publication plays a vital role in recognizing and acknowledging the collaborative nature of research in Natural plants for the treatment of COVID-19-related cases. This co-authorship demonstrates the nature of collaboration and teamwork in scientific research on the subject matter. The figure above shows the most frequent and active experts and reputation researchers with cutting-edge studies on the use of natural plants, and herbal medicines for the treatment of respiratory conditions. This helps current research to identify the extent of research collaboration across pharmaceutical research and toxicity in Natural plants as related to immunity and respiratory illnesses. Future researchers, academic workers, and research institutions can use this co-authorship in building formidable academic networks, and projects, exchange ideas, promote scholarly dialogue, and contribute to the advancement of knowledge. Funding and institutional support for Natural plant-related research are shown. It is

important to note that co-authorship should be based on meaningful contributions to the research project. Ethical considerations, such as proper acknowledgment of contributions, adherence to publication guidelines, and transparency, should be followed to ensure the integrity of co-authorship practices.

Co-authorship/ Organisation full counting

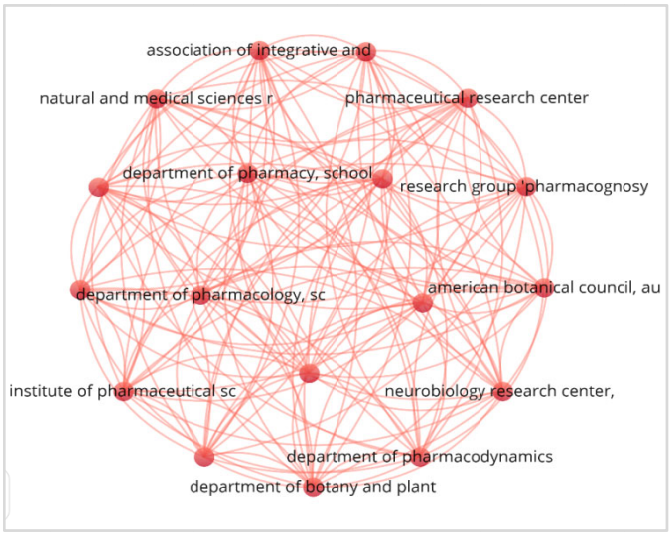


Figure 3.

This search identifies a cluster of 13 items with a total of 153 links. These 13 different organization clusters have a total link strength of 12 each. It is interesting to note that many of these research organizations are from Western countries America and Europe with significant funding, and research interest in Natural plants for pharmaceutical purposes. This extract shows the importance of co-authorship by organizations in ensuring proper attribution and collaboration among researchers in preclinical research. Some of the potential preclinical aspects of the research shown are defining authorship criteriainvolving multidisciplinary teams with individuals contributing in various ways, such as designing experiments, conducting experiments, analyzing data, writing the manuscript, and providing critical input. It also shows the extent of collaboration agreements among researchers in the preclinical research project. The extent of the researcher's communication and coordination depicts the contribution tracking of individual contributions throughout the preclinical research process. Authorship order and the specific role of each researcher in preclinical research promote transparency, collaboration, and proper recognition of contributions. It helps foster a collaborative research environment, ensures fair attribution, and contributes to the integrity of the scientific publication process.

Co-occurrence of all keywords

VOS viewer analysis shows the extent of co-occurrence of keywords whereby only 7 items met the inclusion criteria with 3 significances cluster and 44 total link strength. The co-occurrence of keywords in preclinical research can have several impacts, indicating the relationships, trends, and focus areas within the field. Here are some impacts of the co-occurrence of all keywords in preclinical research. It also identifies research themes by showing the co-occurrence of keywords and helps identify common research themes and topics in preclinical research.

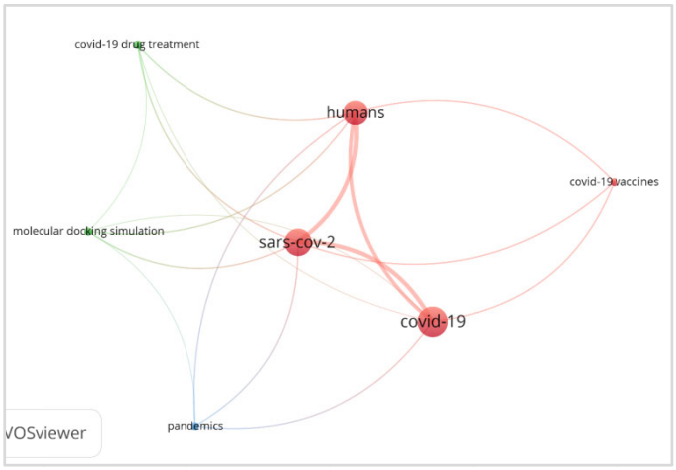


Figure 4.

This analyses which keywords frequently appear together, and researchers can gain insights into the prevalent areas of study within the field. This information can guide researchers in selecting research directions, exploring emerging topics, or understanding the current trends in preclinical research. Co-occurrence similarly maps out the research networks. This co-occurrence has demonstrated the research prioritization and resource allocation in the last few years. The above design shows the co-occurrence of keywords in preclinical research and provides valuable insights into research themes, networks, priorities, and knowledge synthesis. This will aid future researchers and stakeholders in making informed decisions, fostering collaboration, and advancing knowledge in the field of preclinical research.

Co-occurrence of author keyword

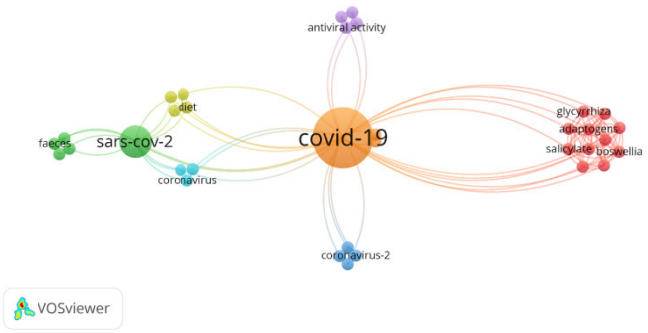


Figure 5

The most frequently discussed themes and their evolution is shown in Figure 5 above. A total of 34 items with 7 clusters met the inclusion. These items generate a total of 123 links while with a non-significant difference of 124 total link strength. COVID-19 is the most frequent theme with 30 co-occurrences, followed by SAR-COV-2 with 13 co-occurrences. Themes such as adaptogen, Boswellia, curcuma, echinacea, Glycyrrhiza, herbal medicine, medicinal fungi, pelargonium, phytotherapy, salicylate, and Sambucus all have single occurrences but since 11 total link strengths.

Conclusion and the Future

Africa has a considerable number of natural plants useful and effective for the treatment of infectious diseases. Although,

there areno specific Natural medicinal plants that have been scientifically proven to be effective in treating COVID-19. However, anecdotal evidence suggests that traditional medicine and herbal remedies are commonly used to manage respiratory illness symptoms and boost immunity. Although, there is sufficient scientific evidence to support the sustainable efficacy of these plant products, however, there is a need for further research to validate their effectiveness against COVID-19. Today, some Natural medicinal plants have been frequently used for treating respiratory illnesses and boosting immunity, however, there are ongoing efforts to ascertain the effectiveness and the potential therapeutic properties of certain Natural plants such as *Sutherlandia frutescens* (Cancer bush) from the indigenous South African plant for treatment of various ailments, including respiratory conditions. Although studies have suggested its potential immunomodulatory and antiviral properties, nevertheless, its effectiveness against COVID-19 has not been scientifically established. Finally, another plant is the *Pelargonium sidoides* (Umckaloabo) which is native to South Africa, and commonly used for respiratory infections. Stack studies suggest its potential effectiveness for antiviral and immunomodulatory activities. However, the nature of its toxicity and usefulness to the human body is yet to be ascertained in preclinical research specifically for COVID-19 cases. Scientific evidence has strongly suggested the need to approach the use of medicinal plants with caution and rely on evidence-based treatments for COVID-19. While traditional knowledge and ethnobotanical practices can provide valuable insights, rigorous scientific studies, including clinical trials, are necessary to establish the safety and efficacy of any treatment. It is advisable to consult with healthcare professionals or regulatory authorities for the most up-to-date and reliable information regarding COVID-19 treatments.

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