ZEUGMA BIOLOGICAL SCIENCE | ZEUGMA BIOLOGICAL SCIENCE | 2024
v:5 n:1 p:1-8

Phytochemicals against COVID-19: Opportunities and Challenges

Yasmeen Junejo[1*], Muhammad Safdar[1], Mehmet Ozaslan[2]
[1]Cholistan University of Veterinary and Animal Sciences, Bahawalpur
[2]Department of Biology, Gaziantep University, Gaziantep, Turkey
yasmeen@cuvas.edu.pk

Abstract

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has an urgent need for effective therapeutic agents. In this regard, phytochemicals, bioactive compounds derived from plants, have emerged as potential candidates for the treatment and prevention of COVID-19. This review explores various facets of phytochemical research in relation to COVID-19, ranging from their identification to future perspectives in their application. It sets the stage, describing their nature, classification, and historical use in traditional medicine, alongside their recognized health benefits. We then delve into the methodologies for phytochemical screening, highlighting advanced techniques such as high-performance liquid chromatography (HPLC) and spectroscopic methods, which are pivotal in identifying and characterizing these compounds. In addition, focusing on potential phytochemicals against SARS-CoV-2, we discuss compounds like flavonoids, terpenoids, and alkaloids, which have shown promise in preliminary studies for their antiviral properties. However, the transition from laboratory findings to clinical applications faces challenges, such as issues of bioavailability, lack of clinical trials, and the complexity of phytochemical interactions. Advancements in nanotechnology for drug delivery, exploration of synergistic effects, and personalized medicine are crucial. Therefore, this review underscores the importance of integrating traditional knowledge with modern scientific studies and highlights the need for inclusive clinical studies to validate the efficacy and safety of phytochemicals. The promising yet challenging path of phytochemical research offers a hopeful path in the ongoing battle against COVID-19 and future pandemics.

Keywords: Phytochemicals; COVID-19; Antiviral Properties; Bioavailability; Clinical Trials.

1. Introduction to Phytochemicals

Phytochemicals, also known as phytonutrients, are a diverse group of chemical compounds produced by plants. They are classified into several categories based on their chemical structure and biological function (Doughari, 2012). Major classes include flavonoids, alkaloids, terpenoids, and phenolic acids (Roy et al., 2019). Each class has its unique characteristics and health benefits. These compounds are found in various parts of plants including fruits, vegetables, grains, nuts, seeds, and leaves. The type and concentration of phytochemicals in a plant depend on the species, part of the plant, and environmental factors. For instance, flavonoids are abundant in berries, tea, and wine (Perez-Vizcaino & Fraga, 2018), while cruciferous vegetables like broccoli are rich in glucosinolates (Herr & Büchler, 2010). Previous studies have shown that phytochemicals have a wide range of health benefits (Leitzmann, 2016; Oomah & Mazza, 1999). They are known for their antioxidant properties, which help in neutralizing harmful free radicals in the body. This can reduce the risk of chronic diseases such

https://doi.org/10.55549/zbs.1416366

as heart disease, diabetes, and cancer. Some phytochemicals also have anti-inflammatory, antimicrobial, and anti-allergic properties (Rakha et al., 2022). Many traditional medicine systems, such as Ayurveda and Traditional Chinese Medicine, have long recognized the importance of phytochemicals (Patwardhan et al., 2005). They use plant-based remedies, which are rich in these compounds, for various therapeutic purposes. The field of phytochemical research is rapidly evolving. Scientists are actively studying the potential of these compounds in preventing and treating various health conditions (Perez-Vizcaino & Fraga, 2018; Rakha et al., 2022; Wong & Chow, 2024). However, challenges remain, such as understanding the bioavailability, efficacy, and safety of phytochemicals when consumed through diet or as supplements.

2. Methodologies for Phytochemical Screening

The methodologies for phytochemical screening involve a range of techniques and processes used to identify and characterize phytochemicals present in plants. These methods are crucial for understanding the potential health benefits of these compounds and for the development of plant-based medicines and supplements.

1. **Extraction Methods**
    a. **Solvent Extraction:** This is the most common method, where solvents like ethanol, methanol, water, or a mixture of solvents are used to extract phytochemicals from plant materials (Pandit & Ansari, 2024).
    b. **Supercritical Fluid Extraction:** This method uses supercritical fluids, typically CO2, under high pressure to extract phytochemicals, offering high purity and yield with minimal solvent residue (Ou et al., 2024).
2. **Qualitative and Quantitative Analysis**
    a. **Thin Layer Chromatography (TLC):** A rapid, simple technique used for the initial screening of phytochemicals. It helps in identifying compounds by their rate of movement on a TLC plate. High-Performance Liquid Chromatography (HPLC): Used for both qualitative and quantitative analysis, HPLC allows for the separation, identification, and quantification of components in a mixture (de Souza et al., 2023).
    b. **Gas Chromatography-Mass Spectrometry (GC-MS):** This method is used for the analysis of volatile compounds and provides information about the molecular weight and structure of the compounds (Cheng et al., 2023).
3. **Spectroscopic Methods:**
    a. **UV-Visible Spectroscopy:** Used for determining the concentration of phytochemicals, especially those with conjugated systems like flavonoids (Wahyuni et al., 2023).
    b. **Fourier Transform Infrared Spectroscopy (FTIR):** Helps in identifying functional groups and understanding the chemical structure of phytochemicals (Arya & Kumar, 2023).
    c. **Nuclear Magnetic Resonance (NMR) Spectroscopy:** Provides detailed information about the molecular structure of phytochemicals (Khalil & Kashif, 2023).

https://doi.org/10.55549/zbs.1416366

4. **Bioassays for Activity Screening**
    a. **Antioxidant Activity Assays:** Methods like DPPH free radical scavenging assay, ABTS assay, and FRAP assay are used to evaluate the antioxidant capacity of phytochemical extracts (Shah & Modi, 2015).
    b. **Antimicrobial Activity Testing:** Methods such as disc diffusion, broth dilution, and agar dilution are employed to screen phytochemicals for antimicrobial properties (Dahiya & Purkayastha, 2012).
5. **Phytochemical Profiling**
    a. **Metabolomics:** An emerging approach that involves the comprehensive analysis of metabolites in a biological sample. It helps in understanding the complete phytochemical profile of a plant extract (Pandohee et al., 2023).

3. Potential Phytochemical Compounds Against SARS-CoV-2

The exploration of potential phytochemical compounds against SARS-CoV-2, the virus responsible for COVID-19, is a significant area of research. Phytochemicals, with their diverse biochemical properties, offer a promising avenue for the development of therapeutic agents.

I. Flavonoids:

a. **Quercetin:** Known for its antiviral properties, Quercetin has shown potential in inhibiting the replication of SARS-CoV-2 in cell culture studies (Derosa et al., 2021).

b. **Epigallocatechin Gallate (EGCG):** Found in green tea, EGCG has demonstrated effectiveness in inhibiting the SARS-CoV-2 main protease, an enzyme critical for viral replication (Ohishi et al., 2022).

II. Terpenoids:

a. **Hesperidin:** A flavanone glycoside, Hesperidin, commonly found in citrus fruits, has been suggested to have potential in blocking the ACE2 receptor, the entry point for SARS-CoV-2 into human cells (Bellavite & Donzelli, 2020).

b. **Glycyrrhizin:** Derived from licorice root, Glycyrrhizin has shown antiviral activity against SARS-CoV and may offer potential against SARS-CoV-2 (van de Sand et al., 2021).

III. Alkaloids:

c. **Berberine:** Found in various plants like Berberis, berberine is known for its anti-inflammatory and immune-modulating properties, which could be beneficial in managing COVID-19 symptoms (Ghareeb et al., 2021).

IV. Phenolic Acids:

a. **Curcumin:** The active compound in turmeric, Curcumin, exhibits anti-inflammatory and antiviral properties. It's being researched for its potential role in modulating the immune response in COVID-19 (Das, 2022).

V. Saponins:

a. **Ginsenosides:** These compounds, found in ginseng, have shown immune-enhancing effects and might be useful in improving the body's response to viral infections, including SARS-CoV-2 (Choi et al., 2022).

https://doi.org/10.55549/zbs.1416366

VI. Tannins:

a. **Punicalagin:** Found in pomegranates, this tannin has displayed antiviral effects against several viruses, although its specific efficacy against SARS-CoV-2 (Chen et al., 2023).

While these phytochemicals show promise, it's important to note that most studies are in preliminary stages, often limited to in vitro (test tube) or computational models. The transition from lab-based research to effective treatments involves extensive clinical trials to assess safety and efficacy in humans. The bioavailability and optimal dosing of these compounds when consumed as part of the diet or as supplements also pose significant challenges.

4. Challenges and Limitations of Phytochemical for COVID-19

The investigation of phytochemicals for the treatment and prevention of COVID-19 presents several challenges and limitations (Hensel et al., 2020; Lim et al., 2021; Yadav & Kaushik, 2021). While the potential of these compounds is promising, there are numerous hurdles in translating laboratory findings into effective, safe, and widely available treatments.

1. **Bioavailability and Absorption:** Many phytochemicals have low bioavailability, meaning they are not easily absorbed or utilized efficiently by the body. This reduces their effectiveness when consumed as part of the diet or as supplements. Modifications to enhance bioavailability can alter the compound's activity or safety profile.
2. **Lack of Clinical Evidence:** Much of the research on phytochemicals and COVID-19 is still in early stages, primarily in vitro (lab-based) or in silico (computer-based) studies. There is a lack of extensive clinical trials to demonstrate efficacy and safety in humans, which is crucial for any potential therapeutic agent.
3. **Complexity of Phytochemical Interactions:** Phytochemicals often work synergistically in their natural form. Isolating individual compounds can diminish their efficacy or lead to unforeseen side effects. Understanding these interactions is complex and requires extensive research.
4. **Standardization and Quality Control:** There's a challenge in standardizing plant extracts, as the concentration of active phytochemicals can vary greatly depending on growing conditions, harvesting methods, and processing techniques. Ensuring consistent quality and concentration in supplements or medicinal products is difficult.
5. **Potential Side Effects and Interactions:** Some phytochemicals may have side effects, especially when taken in high doses or in concentrated forms. They can also interact with conventional medications, potentially leading to adverse effects.
6. **Regulatory and Ethical Issues:** Phytochemical-based treatments require approval from regulatory bodies, which involves a rigorous process to ensure safety and efficacy. Ethical concerns, such as the sustainable and equitable sourcing of plant materials, also need to be addressed.
7. **Variability in Individual Responses:** The efficacy of phytochemicals can vary significantly among individuals due to genetic factors, underlying health conditions, and other variables. Personalized approaches to treatment may be necessary, complicating the use of a one-size-fits-all remedy.

https://doi.org/10.55549/zbs.1416366

5. Future Perspectives and Directions

The future perspectives and directions in the field of phytochemical research, particularly in the context of COVID-19, are dynamic and promising (Newman & Cragg, 2007; Shao & Zhang, 2013).

1. **Advanced Research and Clinical Trials:** Enhanced focus on conducting robust clinical trials to validate the efficacy and safety of phytochemicals against COVID-19. This will help in the translation of laboratory findings to real-world applications. Integration of advanced research methodologies, like AI and machine learning, to predict and analyze the effectiveness of phytochemicals.
2. **Nanotechnology in Drug Delivery:** Employing nanotechnology to improve the bioavailability and targeted delivery of phytochemicals. Nano-encapsulation can protect the active compounds, ensuring they reach the site of action in the body more effectively.
3. **Synergistic Combinations and Phytotherapy:** Exploring synergistic effects of combining multiple phytochemicals or using them alongside conventional treatments. This approach could enhance therapeutic outcomes and reduce side effects. Reviving and integrating traditional phytotherapy knowledge with modern medicine for a more holistic approach to treatment.
4. **Personalized Medicine:** Advancing towards personalized medicine by considering individual variations in genetics, environment, and lifestyle. This approach can optimize phytochemical-based treatments for individuals.
5. **Sustainable and Ethical Sourcing:** Ensuring sustainable and ethical sourcing of plant materials to protect biodiversity and avoid overharvesting of medicinal plants. Developing synthetic or lab-grown alternatives to rare or endangered plant species used in phytochemical production.
6. **Global Collaboration and Knowledge Sharing:** Fostering global collaborations among scientists, researchers, and health professionals to share knowledge, resources, and findings. Encouraging open-access publishing and data sharing to accelerate research and development in this field.
7. **Public Health Policies and Education:** Influencing public health policies to incorporate evidence-based use of phytochemicals in preventing and managing diseases. Enhancing public education and awareness about the benefits and limitations of phytochemicals, promoting informed choices about their use.
8. **Technological Integration in Agriculture:** Using biotechnology and genetic engineering to enhance the production of specific phytochemicals in plants. Implementing precision agriculture techniques to optimize growing conditions for medicinal plants, thereby maximizing phytochemical yield.

Conclusion

In conclusion, phytochemicals present a promising yet challenging frontier in the search for effective treatments against COVID-19. While their potential is emphasized by historical use and preliminary research findings, significant hurdles remain in terms of clinical validation, bioavailability, and safe integration into therapeutic protocols. The future of phytochemical research hinges on a balanced approach that combines traditional wisdom with advanced scientific methodologies, fostering global collaboration and sustainable practices to fully realize their potential in combating current and future health challenges.

https://doi.org/10.55549/zbs.1416366

References

Arya, P., & Kumar, P. (2023). Phytochemical, phase transition, FTIR, and antimicrobial characterization of defatted Trigonella foenum graecum seed extract as affected by solvent polarity. *Journal of Food Measurement and Characterization*, *17*(5), 5234-5246.

Bellavite, P., & Donzelli, A. (2020). Hesperidin and SARS-CoV-2: New light on the healthy function of citrus fruits. *Antioxidants*, *9*(8), 742.

Chen, H.-F., Wang, W.-J., Chen, C.-Y., Chang, W.-C., Hsueh, P.-R., Peng, S.-L., Wu, C.-S., Chen, Y., Huang, H.-Y., & Shen, W.-J. (2023). The natural tannins oligomeric proanthocyanidins and punicalagin are potent inhibitors of infection by SARS-CoV-2. *eLife*, *12*, e84899.

Cheng, H., Mei, J., & Xie, J. (2023). Analysis of key volatile compounds and quality properties of tilapia (Oreochromis mossambicus) fillets during cold storage: Based on thermal desorption coupled with gas chromatography-mass spectrometry (TD-GC-MS). *LWT*, *184*, 115051.

Choi, J. H., Lee, Y. H., Kwon, T. W., Ko, S.-G., Nah, S.-Y., & Cho, I.-H. (2022). Can Panax ginseng help control cytokine storm in COVID-19? *Journal of Ginseng Research*, *46*(3), 337-347.

Dahiya, P., & Purkayastha, S. (2012). Phytochemical screening and antimicrobial activity of some medicinal plants against multi-drug resistant bacteria from clinical isolates. *Indian journal of pharmaceutical sciences*, *74*(5), 443.

Das, K. (2022). Herbal plants as immunity modulators against COVID-19: A primary preventive measure during home quarantine. *Journal of Herbal Medicine*, *32*, 100501.

de Souza, A. L. C., do Rego Pires, A., Moraes, C. A. F., de Matos, C. H. C., dos Santos, K. I. P., Campos e Silva, R., Acuña, S. P. C., & dos Santos Araújo, S. (2023). Chromatographic Methods for Separation and Identification of Bioactive Compounds. In *Drug Discovery and Design Using Natural Products* (pp. 153-176). Springer.

Derosa, G., Maffioli, P., D'Angelo, A., & Di Pierro, F. (2021). A role for quercetin in coronavirus disease 2019 (COVID-19). *Phytotherapy Research*, *35*(3), 1230-1236.

Doughari, J. H. (2012). *Phytochemicals: extraction methods, basic structures and mode of action as potential chemotherapeutic agents*. INTECH Open Access Publisher Rijeka, Croatia.

Ghareeb, D. A., Saleh, S. R., Seadawy, M. G., Nofal, M. S., Abdulmalek, S. A., Hassan, S. F., Khedr, S. M., AbdElwahab, M. G., Sobhy, A. A., & Abdel-Hamid, A. s. A. (2021). Nanoparticles of ZnO/Berberine complex contract COVID-19 and respiratory co-bacterial infection in addition to elimination of hydroxychloroquine toxicity. *Journal of Pharmaceutical Investigation*, *51*, 735-757.

Hensel, A., Bauer, R., Heinrich, M., Spiegler, V., Kayser, O., Hempel, G., & Kraft, K. (2020). Challenges at the Time of COVID-19: Opportunities and Innovations in Antivirals from Nature. *Planta medica*, *86*(10), 659-664.

Herr, I., & Büchler, M. W. (2010). Dietary constituents of broccoli and other cruciferous vegetables: implications for prevention and therapy of cancer. *Cancer treatment reviews*, *36*(5), 377-383.

https://doi.org/10.55549/zbs.1416366

Khalil, A., & Kashif, M. (2023). Nuclear magnetic resonance spectroscopy for quantitative analysis: a review for its application in the chemical, pharmaceutical and medicinal domains. *Critical Reviews in Analytical Chemistry*, *53*(5), 997-1011.

Leitzmann, C. (2016). Characteristics and health benefits of phytochemicals. *Complementary Medicine Research*, *23*(2), 69-74.

Lim, X. Y., Teh, B. P., & Tan, T. Y. C. (2021). Medicinal plants in COVID-19: potential and limitations. *Frontiers in pharmacology*, *12*, 611408.

Newman, D. J., & Cragg, G. M. (2007). Natural products as sources of new drugs over the last 25 years. *Journal of natural products*, *70*(3), 461-477.

Ohishi, T., Hishiki, T., Baig, M. S., Rajpoot, S., Saqib, U., Takasaki, T., & Hara, Y. (2022). Epigallocatechin gallate (EGCG) attenuates severe acute respiratory coronavirus disease 2 (SARS-CoV-2) infection by blocking the interaction of SARS-CoV-2 spike protein receptor-binding domain to human angiotensin-converting enzyme 2. *PLoS One*, *17*(7), e0271112.

Oomah, B. D., & Mazza, G. (1999). Health benefits of phytochemicals from selected Canadian crops. *Trends in food science & technology*, *10*(6-7), 193-198.

Ou, H., Zuo, J., Gregersen, H., & Liu, X.-Y. (2024). Combination of supercritical CO2 and ultrasound for flavonoids extraction from Cosmos sulphureus: Optimization, kinetics, characterization and antioxidant capacity. *Food Chemistry*, *435*, 137598.

Pandit, M. A., & Ansari, T. (2024). Extraction Methods Of Polyphenol Derivative (Flavonoid). In *The Flavonoids* (pp. 59-78). Apple Academic Press.

Pandohee, J., Kyereh, E., Kulshrestha, S., Xu, B., & Mahomoodally, M. F. (2023). Review of the recent developments in metabolomics-based phytochemical research. *Critical Reviews in Food Science and Nutrition*, *63*(19), 3734-3749.

Patwardhan, B., Warude, D., Pushpangadan, P., & Bhatt, N. (2005). Ayurveda and traditional Chinese medicine: a comparative overview. *Evidence-based complementary and alternative medicine*, *2*, 465-473.

Perez-Vizcaino, F., & Fraga, C. G. (2018). Research trends in flavonoids and health. *Archives of biochemistry and biophysics*, *646*, 107-112.

Rakha, A., Umar, N., Rabail, R., Butt, M. S., Kieliszek, M., Hassoun, A., & Aadil, R. M. (2022). Anti-inflammatory and anti-allergic potential of dietary flavonoids: A review. *Biomedicine & Pharmacotherapy*, *156*, 113945.

Roy, M., Datta, A., Roy, M., & Datta, A. (2019). Fundamentals of phytochemicals. *Cancer Genetics and Therapeutics: Focus on Phytochemicals*, 49-81.

Shah, P., & Modi, H. (2015). Comparative study of DPPH, ABTS and FRAP assays for determination of antioxidant activity. *Int. J. Res. Appl. Sci. Eng. Technol*, *3*(6), 636-641.

Shao, L., & Zhang, B. (2013). Traditional Chinese medicine network pharmacology: theory, methodology and application. *Chinese journal of natural medicines*, *11*(2), 110-120.

van de Sand, L., Bormann, M., Alt, M., Schipper, L., Heilingloh, C. S., Steinmann, E., Todt, D., Dittmer, U., Elsner, C., & Witzke, O. (2021). Glycyrrhizin effectively inhibits SARS-CoV-2 replication by inhibiting the viral main protease. *Viruses*, *13*(4), 609.

https://doi.org/10.55549/zbs.1416366

Wahyuni, P. D., Candra, I. P., & Singapurwa, N. M. A. S. (2023). Identification of Phytochemical Compounds and Antioxidant Activity in Methanol Extract of Basa Genep Seasoning. *International Journal of Scientific Multidisciplinary Research*, *1*(11), 1375-1388.

Wong, Y. Y., & Chow, Y. L. (2024). Exploring the potential of spice-derived phytochemicals as alternative antimicrobial agents. *eFood*, *5*(1), e126.

Yadav, V., & Kaushik, P. (2021). Phytochemicals against COVID-19 and a gap in clinical investigations: An outlook. *Indian Journal of Biochemistry and Biophysics (IJBB)*, *58*(5), 403-407.

https://doi.org/10.55549/zbs.1416366