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Unlocking the Potential of Curcumin: A Mini-Review of Its Anti-inflammatory Properties in COVID-19 Patients

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Abstract

Introduction: *Viral diseases are a current concern around the world. Treatment alternatives are a field of growing interest in treating these diseases. Curcumin has already proven effective and is known for its anti-inflammatory properties in vitro; however, the impact of this natural compound in the clinical setting needs to be clarified, especially in the use of COVID-19 disease.*

Methods: *A systematic search was conducted in PubMed using MeSH terms in August 2023. All selected articles were randomized clinical trials that evaluated the anti-inflammatory effect of curcumin in patients with acute-stage COVID-19 viral diseases in people over 18 years of age. The research was conducted using MeSH terms.*

Results: *413 studies were identified, of which only 4 met the inclusion criteria. It was shown that curcumin reduces inflammatory markers in patients with COVID-19 in the acute phase.*

Discussion: *Despite evidence of improvement of inflammatory markers of curcumin in subjects with COVID-19, the clinical utility is still unknown because most trials did not describe clinical outcomes.*

Conclusion: *Although curcumin is a promising anti-inflammatory resource, more stringent clinical trials with well-defined results are needed to evaluate the effect of curcumin on clinical outcomes—additionally, strict protocols to control bias.*

Introduction

The incidence of infectious diseases of viral origin has increased exponentially recently, primarily due to the COVID-19 pandemic. These increased incidences of acute infectious diseases are associated with further growth in healthcare costs, a negative impact on quality of life, and, for some infections, might even be associated with a concern about case fatality (Hui EK, 2006). ; Martínez G,2011: Dronina et al, 2021).

Given the lack of symptomatic and curative treatment alternatives, there is a growing need to explore new treatment options with a particular interest in natural compounds that have recently taken the lead.

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Among those alternatives, curcumin, the ingredient in turmeric, has quickly come to attention as its various properties offer a novel, low-risk alternative approach to tackling infectious diseases (Dei Cas, 2019).

Currently, several studies provide a biological basis for the potential of curcumin in the context of viral infections. They could explain the biological basis of curcumin for viral diseases, but its effect on human metabolism and anti-inflammatory response needs to be clarified. Therefore, this mini-review aims to identify the current scientific knowledge in the literature on the use of curcumin and explore its potential as an anti-inflammatory in patients with COVID-19 in the acute phase.

Materials and Methods

Search strategy

In August 2023, an online search was conducted in the PubMed database using the following research question: "What are the anti-inflammatory effects of curcumin in patients with acute COVID-19?"

After the article search, the articles were selected under the selection criteria, first according to title and abstract and then the full text of the remaining articles. The researchers carried out the process independently, and discrepancies were resolved.

The study focused on the population over 18 with COVID-19 disease in the acute phase. Clinical trials that used curcumin in their intervention group were evaluated. On the other hand, the results that evaluated changes in pro-inflammatory and inflammatory markers were analyzed.

Data collection

The Pubmed database was used to search for clinical trials written in English and published between 2020 and 2023. We used the Mesh terms presented in Appendix 1.

Selection criteria

The selection criteria were based on (1) intervention: curcumin in any form, not combined; (2) disease: COVID-19 infectious viral disease in the acute phase; (3) anti-inflammatory effect; and (4) population: patients older than 18 years.

Titles and abstracts were screened to eliminate duplicates, articles in languages other than English, non-clinical trials, and studies evaluating viral diseases unrelated to COVID-19. Figure 1 details the research process.

Results

A total of 413 articles were identified, of which 398 were ineligible using automation tools. Therefore, 15 articles were obtained, of which nine were excluded due to title and abstract, and two did not meet the inclusion criteria. In total, four articles were analyzed.

The potentials of curcumin in treating COVID-19 in the acute phase were evaluated, focusing on the decrease in pro-inflammatory markers.

A study conducted by Valizadeh et al. evaluated the effects of curcumin on COVID-19 viral mRNA expression and serum levels of pro-inflammatory cytokines IL-1β, IL-6, TNF-α, and IL-18. This trial enrolled 40 COVID-19 patients and 40 healthy controls, randomized in a 1:1 ratio to receive nano-curcumin 160 mg or placebo. The authors reported a decrease in viral mRNA expression and also similar decreases in levels of IL-1β, IL-6, TNF-α, and IL-18 among infected participants that received curcumin when compared to those allocated to the control group ($p = 0.0041$, 0.0001, 0.0013 and 0.0045, respectively) (Valizadeh et al., 2020).

Hassaniazad et al. conducted a triple-blind placebo-controlled trial in 40 individuals diagnosed with COVID-19. The intervention was nano curcumin 40 mg twice daily for two weeks. They reported a reduction in the serum levels of IFN-γ ($p = 0.52$) and IL-17 ($p = 0.11$), along with increased levels of IL-4 ($p = 0.12$) and TGF-β ($p = 0.14$) when compared to the placebo group. Furthermore, after seven days of therapy, gene expression of TBX21 ($p = 0.02$) was consistently decreased while expression of FOXP3 increased significantly ($p = 0.005$). Regarding the safety of nano-curcumin, it was shown to be a safe supplement without specific adverse reactions. (Hassaniazad et al., 2021).

Asadirad et al. evaluated the impact of nano-curcumin on the inflammatory cytokines in mild-to-moderate hospitalized COVID-19 patients through a randomized, open-label, placebo-controlled clinical trial. This trial enrolled 60 mild-to-moderate hospitalized COVID-19 patients divided into two groups. The treatment arm received nano-curcumin 240 mg/day for seven days, and the control group received a placebo. The authors reported a decrease in the expression of IFN-γ ($p = 0.006$) and TNF-α ($p = 0.04$) among patients who received nano curcumin (Asadirad et al., 2022).

Sadeghizadeh et al. evaluated the anti-inflammatory power of nano curcumin in patients hospitalized with COVID-19 and receiving treatment for this disease. This clinical trial included 42 patients: 21 in the treatment arm with 140 mg of curcumin + treatment COVID-19 (Hydroxychloroquine + sofosbuvir) and 21 in placebo + therapy COVID-19

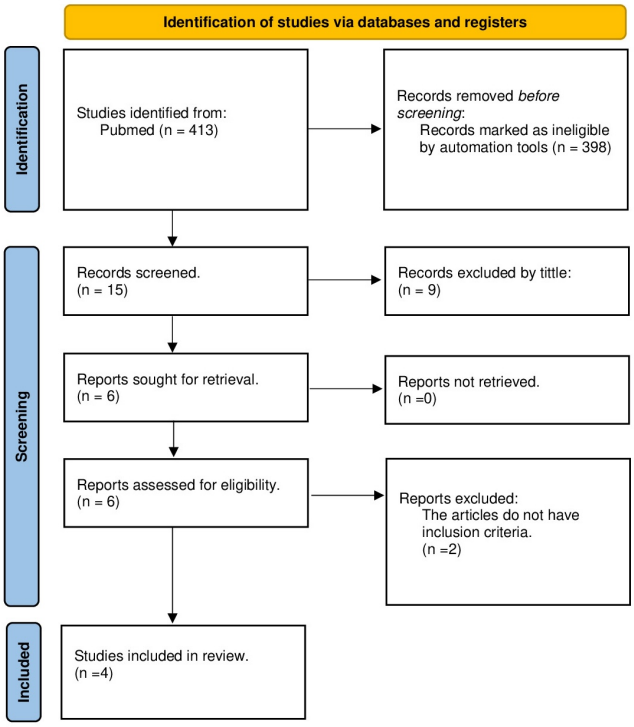

Figure 1: *Research process.*

(Hydroxychloroquine + sofosbuvir). Patients from the nano-curcumin group showed decreased levels of inflammatory markers after 14 days of treatment compared to the control group [IL-6 (p=0.0002), IL-10 (p=0.018)]. The levels of IL8 decreased but without significant statistics (P=0.1154) (Sadeghizadeh et al., 2023).

Discussion

Curcumin has long been studied as a possible intervention to treat viral diseases, not only for its direct antiviral effects but also for its anti-inflammatory properties. In recent years, and mainly due to the COVID-19 pandemic, alternative and complementary treatments for viral infections have gained particular relevance among the medical community. In that sense, curcumin is one of the compounds under the spotlight. However, the results of studies applying different formulations of curcumin should be taken with caution.

Nano curcumin, a modified compound of the curcumin native powder with increased bioavailability, was used as the intervention of the analyzed studies.

The studies conducted by Valizadeh et. Al., Fessler et. Al., Hassaniazad et. Al., and Asadirad et. Al. and Sadeghizadeh et al. reported significant results regarding the effects of curcumin, or in this case, nano curcumin, on serum levels of pro-inflammatory markers in patients diagnosed with COVID-19. Regarding the reporting of adverse effects (AE), the Hassaniazad et al. study reported that no AEs were detected, and Sadeghizadeh et al. said that no AEs were detected in the liver, gallbladder, or blood; the rest of the studies did not mention EA.

The major limitation of these trials is that clinical outcomes were not contemplated. Such analyses are, therefore, inherently limited as laboratory data is not guaranteed to promote clinically significant benefits.

Another area for improvement from available evidence can be perceived concerning sample sizes. Most studies analyzed here included very few subjects, with selection criteria and attrition bias being significant concerns. Hassaniazad et. Al., for instance, did not declare if the enrolled subjects were vaccinated when the trial was conducted. Furthermore, curcumin in the nano curcumin format was given at different doses, lapses, and formulations, likely due to poor standardization for the intervention, as it is indeed a novel compound in clinical practice. Considering the different pharmacodynamics of drug formulations, this could have introduced bias into the results.

Conclusion

The reviewed studies provided valuable insight into the multifactorial effects of curcumin on proinflammatory markers in patients with COVID-19. Evi-

dence suggests that nano curcumin shows promise in mitigating the inflammatory response associated with COVID-19 in the acute phase. In particular, nano curcumin appears to modulate several proinflammatory cytokines and immune responses.

Additionally, our study searched for articles in English, potentially limiting the inclusion of studies in other languages. It is essential to recognize the limitations of some of these studies, including small sample sizes, which may affect the generalizability of our results. Further research with larger sample sizes, standardized protocols, and comprehensive clinical outcome assessments is needed to understand better curcumin's potential benefits and limitations in treating viral diseases.

While our findings suggest that nano curcumin's anti-inflammatory properties warrant further investigation, it is crucial to be mindful of these limitations. Overcoming these challenges and conducting future research with more robust methodologies will be essential to determine the true therapeutic potential of curcumin in the battle against COVID-19 and other viral diseases.

Appendices

Appendix 1. MeSH terms

((curcumin) OR (1,6-Heptadiene-3,5-dione, 1,7-bis 4-hydroxy- 3-methoxyphenyl) OR (Turmeric Yellow) OR (Yellow, Turmeric) OR (Curcumin Phytosome) OR (Phytosome, Curcumin) OR (Diferuloylmethane) OR (Mervia) OR (Curcumas) OR (Curcuma zedoaria) OR (Curcuma zedoarias) OR (Curcuma longa) OR (Tumeric)) AND ((Diseases, Virus) OR (Disease, Virus) OR (Virus Disease) OR (Virus Infections) OR (Infection, Virus) OR (Infections, Virus) OR (Virus Infection) OR (Viral Diseases) OR (Disease, Viral) OR (Diseases, Viral) OR (Viral Disease) OR (Viral Infections) OR (Infection, Viral) OR (Infections, Viral) OR (viral Infection)) AND ((Anti Inflammatory Agents) OR (Antiinflammatory Agent) OR (Agent, Antiinflammatory) OR (Antiinflammatory Agents) OR (Agents, Antiinflammatory) OR (Anti-Inflammatories) OR (Anti Inflammatories) OR (Anti-inflammatories) OR (Anti-Inflammatory Agent) OR (Agent, Anti- Inflammatory) OR (Anti Inflammatory Agent) OR (Agents, Anti- Inflammatory) OR (Agents, Anti Inflammatory) OR (COVID-19))Filters: Clinical Trial,Randomized Controlled Trial, in the last 5 years Sort by: Most Recent.

Author Contributions

All the authors contribute in the selection of the topic, methods selection, reviewing the articles, and writing of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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