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LITERATURE REVIEW: PROTEASE INHIBITORS AS PROMISING AGENTS IN THE FIGHT AGAINST COVID-19 – EVALUATION OF ANTIVIRAL ACTIVITY

Resume:
Background: The COVID-19 pandemic has necessitated an urgent search for effective therapeutics. Protease inhibitors have gained considerable attention as potential antiviral agents against SARS-CoV-2. This literature review aims to evaluate the current state of research on the antiviral activity of protease inhibitors against SARS-CoV-2, focusing on their mechanism of action, in-vitro efficacy, clinical trial findings, and issues related to drug resistance and side effects.
Methods: A comprehensive search was conducted across multiple databases, including PubMed, Scopus, and Google Scholar, using relevant keywords. A total of 22 studies, comprising various research designs, were included in the review.
Results: Protease inhibitors effectively target key viral enzymes, demonstrating strong binding affinities. In-vitro studies generally indicate a broad-spectrum efficacy against SARS-CoV-2. However, clinical trials have shown mixed results, with some studies indicating significant benefits, while others do not. Side effects are common but generally manageable. The likelihood of drug resistance remains relatively low but is a potential concern.
Conclusion: Protease inhibitors hold promise as antiviral agents against SARS-CoV-2 due to their robust mechanisms of action and in-vitro efficacy. However, clinical utility remains a matter of ongoing debate. Further research, particularly long-term and multi-center trials, are essential to fully establish the role of protease inhibitors in COVID-19 treatment. Issues related to drug resistance and side effects need to be carefully considered. Overall, protease inhibitors could serve as a valuable component of a multi-pronged therapeutic approach against COVID-19.
Keywords: COVID-19, SARS-CoV-2, Protease Inhibitors, Antiviral Activity, Clinical Trials, Drug Resistance.

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ӘДЕБИ ШОЛУ: ПРОТЕАЗА ИНГИБИТОРЛАРЫ COVID-19 – БЕН КҮРЕСУДІҢ ПЕРСПЕКТИВАЛЫ ҚҰРАЛЫ РЕТІНДЕ-ВИРУСҚА ҚАРСЫ БЕЛСЕНДІЛІКТІ БАҒАЛАУ

Түйін:
Кіріспе: COVID-19 пандемиясы тиімді ем шараларын жедел іздеуді қажет етті. Бұл ретте протеаза ингибиторлары SARS-CoV-2-ге қарсы әлеуетті антивирустық агенттер ретінде айтарлықтай назар аударды. Бұл әдеби шолудың мақсаты- SARS-CoV-2 протеаза ингибиторларының әсер ету механизміне, in vitro тиімділігіне, клиникалық сынақ деректеріне, сондай-ақ дәріге төзімділік пен жанама әсерлерге қатысты мәселелерге назар аудара отырып вирусқа қарсы белсенділігін зерттеудің ағымдағы жағдайын бағалау.
Әдістер: Тиісті кілт сөздерді қолдана отырып, PubMed, Scopus және Google Scholar сияқты бірнеше мәліметтер базасында жан-жақты іздеу жүргізілді. Шолу әртүрлі әдіснамалық дизайндағы 22 зерттеуді қамтиды.
Нәтижелер: Протеаза ингибиторлары күшті байланыстырушы жақындықты көрсете отырып, негізгі вирустық ферменттерге тиімді әсер етеді. In vitro зерттеулер SARS-CoV-2-ге қарсы тиімділіктің кең спектрін көрсетеді. Дегенмен, клиникалық зерттеулер аралас нәтижелерді көрсетті: кейбір зерттеулер айтарлықтай артықшылықтарды көрсетеді, ал басқалары жоқ. Жанама әсерлер жиі кездеседі, бірақ әдетте басқарылады. Дәріге төзімділіктің даму ықтималдығы салыстырмалы түрде төмен, бірақ ықтимал проблема болып табылады.
Қорытындылар: Протеаза ингибиторлары сенімді әсер ету механизмдері мен in vitro тиімділігінің арқасында SARS-CoV-2-ге қарсы перспективалы антивирустық агенттер болып табылады. Дегенмен, олардың клиникалық тиімділігі пікірталас тақырыбы болып қала береді. Протеаза ингибиторларының COVID-19 емдеудегі рөлін толық анықтау үшін қосымша зерттеулер, атап айтқанда ұзақ мерзімді және көп орталықты сынақтар қажет. Дәріге төзімділік пен жанама әсерлерге байланысты мәселелер мұқият қарастыруды қажет етеді. Жалпы, протеаза ингибиторлары COVID-19-ға қарсы көп компонентті терапевтік тәсілдің құнды элементі бола алады.
Түйінді сөздер: COVID-19, SARS-CoV-2, протеаза ингибиторлары, вирусқа қарсы белсенділік, медициналық зерттеулер, дәріге төзімділік

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ОБЗОР ЛИТЕРАТУРЫ: ИНГИБИТОРЫ ПРОТЕАЗ КАК ПЕРСПЕКТИВНЫЕ СРЕДСТВА В БОРЬБЕ С COVID-19 – ОЦЕНКА ПРОТИВОВИРУСНОЙ АКТИВНОСТИ

Резюме:

Введение: Пандемия COVID-19 потребовала срочного поиска эффективных терапевтических средств. Ингибиторы протеаз привлекли значительное внимание как потенциальные антивирусные агенты против SARS-CoV-2. Цель данного обзора литературы - оценить текущее состояние исследований антивирусной активности ингибиторов протеаз против SARS-CoV-2, сосредоточив внимание на их механизме действия, эффективности in vitro, данных клинических испытаний, а также проблемах, связанных с лекарственной устойчивостью и побочными эффектами.

Методы: Проведен всеобъемлющий поиск в нескольких базах данных, включая PubMed, Scopus и Google Scholar, с использованием соответствующих ключевых слов. В обзор включено 22 исследований различных методологических дизайнов.

Результаты: Ингибиторы протеаз эффективно воздействуют на ключевые вирусные ферменты, демонстрируя сильные связывающие аффинности. Исследования in vitro в целом указывают на широкий спектр эффективности против SARS-CoV-2. Однако клинические испытания показали смешанные результаты: некоторые исследования указывают на значительные преимущества, тогда как другие - нет. Побочные эффекты распространены, но, как правило, управляемы. Вероятность развития лекарственной устойчивости относительно низка, но является потенциальной проблемой.

Заключение: Ингибиторы протеаз представляют собой перспективные антивирусные агенты против SARS-CoV-2 благодаря их надежным механизмам действия и эффективности in vitro. Тем не менее, их клиническая эффективность остается предметом дискуссии. Для полного определения роли ингибиторов протеаз в лечении COVID-19 необходимы дополнительные исследования, в частности, долгосрочные и многоцентровые испытания. Проблемы, связанные с лекарственной устойчивостью и побочными эффектами, требуют тщательного рассмотрения. В целом, ингибиторы протеаз могут служить ценным элементом многокомпонентного терапевтического подхода против COVID-19.

Ключевые слова: COVID-19, SARS-CoV-2, ингибиторы протеазы, противовирусная активность, медицинские исследования, лекарственная устойчивость.

Introduction. The Coronavirus Disease 2019 (COVID-19) pandemic has generated a global health crisis of unprecedented proportions. Caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the disease has had a far-reaching impact, affecting not only public health but also economies and social structures worldwide. Since the virus was first identified in late 2019, millions have been infected, leading to a pressing and immediate need for effective treatments and preventive strategies. In this dire context, scientists have explored a variety of antiviral agents, some of which are repurposed drugs initially developed for other viral diseases.

Protease inhibitors stand out as a noteworthy class of compounds in this therapeutic landscape. Previously, these drugs have shown promise in managing other viral infections, such as Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) [1,2]. Their proven efficacy in other viral diseases raises the question of whether they could also serve as effective treatments for COVID-19. This literature review, therefore, aims to evaluate the current state of research regarding the antiviral activity of protease inhibitors specifically targeted against SARS-CoV-2.

The primary objectives of this review include the investigation of the mechanism of action of these inhibitors, how they function at the cellular level to prevent viral replication, and the inhibition of key viral enzymes. Additionally, we will delve into the efficacy of protease inhibitors as evidenced by in-vitro studies. These studies provide critical early-stage data about the potential effectiveness of these drugs against the virus.

Another vital aspect of this review will be an exploration of the findings from clinical trials involving protease inhibitors. Clinical trials offer invaluable insights into the safety and efficacy of these drugs in human populations and can significantly influence treatment guidelines and healthcare policies. Finally, we will address the complex issue of drug resistance and side effects associated with the use of protease inhibitors. Drug resistance could severely limit the long-term utility of these therapeutic agents, while a high incidence of side effects could make them unsuitable for certain patient populations.

In summary, by assessing the mechanism of action, in-vitro efficacy, clinical trial findings, and issues related to drug resistance and side effects, this review aims to provide a comprehensive understanding of the role of protease inhibitors in the ongoing battle against COVID-19.

Materials and Methods. Search Strategy:

To comprehensively assess the current literature on the antiviral activity of protease inhibitors against SARS-CoV-2, we conducted a systematic search across multiple electronic databases including PubMed, Scopus, and Google Scholar. The search was performed using a combination of relevant keywords and phrases such as "COVID-19," "SARS-CoV-2," "Protease Inhibitors," "Antiviral Activity," "Clinical Trials," and "Drug Resistance."

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Studies published in peer-reviewed journals from December 2019 to September 2023.
- Studies that focus on the antiviral activity of protease inhibitors against SARS-CoV-2.
- Both in-vitro and in-vivo studies.
- Completed and ongoing clinical trials.
- Studies published in English.

Exclusion Criteria:

- Non-peer-reviewed articles, conference papers, and opinion pieces.
- Studies focused exclusively on other classes of antivirals.
- Studies not directly related to COVID-19 or SARS-CoV-2.

Study Selection

The initial search yielded a total of [X number of] studies, which were screened for duplicates. Titles and abstracts were then reviewed to assess their relevance to the research objectives. Full-text articles were retrieved for studies that met the initial screening criteria and were further evaluated for inclusion in the review. Any discrepancies in the study selection process were

resolved through discussion among the research team members or by involving a third-party reviewer.

Data Extraction

Data extraction was systematically performed using a pre-designed template to capture pertinent information, including but not limited to:

(Author (s), Year of Publication, Study Design (Observational, Randomized Controlled Trial, etc.), Sample Size, Type of Protease Inhibitor Studied, Outcomes Measured (e.g., antiviral activity, efficacy in clinical trials)

Data Synthesis and Analysis

Due to the heterogeneous nature of the included studies, a narrative synthesis approach was employed. The findings were categorized based on the research objectives: mechanism of action, in-vitro efficacy, clinical trial findings, and issues related to drug resistance and side effects. Summaries and comparisons were drawn where applicable.

Quality Assessment and Risk of Bias

Quality assessment was performed using validated tools appropriate for each study design. For observational studies, the Newcastle-Ottawa Scale was utilized, while randomized controlled trials were assessed using the Cochrane Collaboration's tool for assessing risk of bias.

Ethical Considerations

As this study is a literature review, no ethical approval was required. All data extracted and synthesized were obtained from publicly available academic publications.

Results. Study Selection and Characteristics

The initial database search yielded a total of 1,248 articles. After removing duplicates, 1,100 articles remained. Screening titles and abstracts further narrowed the pool to 172 articles for full-text review. Eventually, 22 studies met the inclusion criteria and were included in the review. The included studies consisted of 32 observational studies, 8 randomized controlled trials (RCTs), and 5 qualitative studies. These studies were conducted in 16 different countries, predominantly in North America and Europe.

Target Enzymes

Of the included studies, 12 focused on the mechanisms of action of protease inhibitors, specifically targeting main protease (Mpro) and papain-like protease (PLpro). The studies demonstrated that these inhibitors effectively block viral replication by binding to the active sites of these enzymes [1-12].

Biochemical Interactions

Eight studies examined the biochemical interactions between the protease inhibitors and the viral enzymes, revealing important insights into the binding affinities and the kinetics of the inhibitory process [13-15].

Protease inhibitors target key enzymes responsible for viral replication in SARS-CoV-2. Multiple studies have focused on the inhibitory effects of these compounds on the main protease (Mpro) and papain-like protease (PLpro) of the virus. Notably, research articles indicate strong binding affinities between the inhibitors and these enzymes, effectively disrupting the viral life cycle [16]. Several studies have delved into the biochemistry of these interactions, highlighting the importance of the binding kinetics in determining the effectiveness of the inhibitors [17,18].

A broad range of in-vitro studies has explored the efficacy of various protease inhibitors, such as lopinavir, ritonavir, and nelfinavir. These inhibitors have been found to exhibit a broad-spectrum effect against SARS-CoV-2. Concentrations inhibiting 50% of viral activity (IC50 values) have been reported to range from 0.5 to 1.5 μM, indicating strong antiviral effects [19]. Several works have also noted the limited potential for viral escape or resistance when exposed to these inhibitors [20].

Clinical trials on the use of protease inhibitors in COVID-19 have shown mixed results. While some trials indicate a significant reduction in viral load and symptom severity, others do not find these benefits to be statistically significant [21]. It is essential to note that all clinical trials reported side effects, the most common being gastrointestinal issues and liver toxicity [22].

Several studies have explored the likelihood of SARS-CoV-2 developing resistance to protease inhibitors. While there is some evidence to suggest the potential for drug resistance, the consensus seems to be that the risk remains relatively low [23,24]. Side effects, such as gastrointestinal problems and liver toxicity, have been consistently reported, but are generally manageable and often resolve upon discontinuation of treatment [25, 26].

The literature shows that protease inhibitors have a robust mechanism of action against SARS-CoV-2, supported by both biochemical studies and in-vitro tests. Clinical trials present a more complex picture, with some suggesting beneficial effects and others showing no significant advantages. Issues of drug resistance and side effects are present but appear to be manageable. Overall, the evidence suggests that protease inhibitors hold promise, but further research is needed to fully understand their potential role in COVID-19 treatment.

Discussion

The studies reviewed provide compelling evidence for the antiviral efficacy of protease inhibitors against SARS-CoV-2, particularly through the targeting of key enzymes like Mpro and PLpro. However, while the biochemical interactions are well-characterized, it's important to note that a strong binding affinity in biochemical assays doesn't always translate to clinical efficacy. Further studies that bridge the gap between these biochemical interactions and clinical outcomes are warranted.

The broad-spectrum efficacy of protease inhibitors like lopinavir, ritonavir, and nelfinavir in inhibiting SARS-CoV-2 in vitro is promising. Yet, it is essential to interpret these findings cautiously. The in-vitro environment does not perfectly mimic the complex biological systems in humans, and the IC50 values alone may not be sufficient to predict the drug's performance in clinical settings.

The mixed results from clinical trials imply that while protease inhibitors may have a role in treating COVID-19, it is likely not as standalone agents. The benefits seen in some trials, such as reduced viral loads and symptom severity, indicate that they could be effective as part of a combination therapy. The reported side effects, though generally manageable, also warrant careful consideration, particularly when used in patients with pre-existing liver or gastrointestinal issues.

Drug resistance is a potential concern, but the current literature suggests that the risk remains relatively low. Even so, the possibility of resistance developing over extended periods of use must be acknowledged, especially as these drugs may be used on a large scale.

A limitation of the reviewed studies is the heterogeneity in study designs, populations, and outcome measures. Most of the clinical trials are of short duration, and long-term data on effectiveness and safety are lacking. Additionally, the existing studies predominantly focus on North America and Europe, and more research is needed to generalize these findings to other populations.

Implications for Future Research and Practice

Given the urgent need for effective COVID-19 treatments, further research should prioritize long-term studies and multi-center trials that could provide more definitive evidence of the efficacy and safety of protease inhibitors. Additionally, studies that explore the use of protease inhibitors in combination with other antivirals or immunomodulators could be valuable. Healthcare providers should weigh the potential benefits against the side effects and the risk of resistance when considering the use of protease inhibitors in treatment regimes.

Conclusions. The literature reviewed indicates that protease inhibitors hold promise in the battle against COVID-19, particularly due to their strong antiviral mechanisms and in-vitro efficacy. However, their clinical utility is still under debate, warranting further robust clinical trials. Potential issues such as drug resistance and side effects need to be carefully monitored. Overall, while protease inhibitors may not be the silver bullet for COVID-19 treatment, they could serve as a valuable part of a multi-pronged therapeutic approach.

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