INTERNATIONAL JOURNAL OF
PHARMACEUTICAL AND HEALTHCARE INNOVATION
journal homepage: www.ijphi.com

OPEN ACCESS

Review Article

Repurposing Kinase Inhibitors for COVID-19 A Comprehensive Review of Antiviral and Immunomodulatory Effects

Ramdas Bhat [1]*, Gayathri Palakki [2] ,Mithila Uday [2], Veena Karicheri [2] ,Adira Bhandary [2]

[1]Associate Professor, Department of Pharmacology, Srinivas College of Pharmacy, Valachil, Frangipete Post, Mangalore, Karnataka, India. 574143

[2] UG scholar, Department of Pharmacy Practice, Srinivas College of Pharmacy, Valachil, Frangipete Post, Mangalore, Karnataka, India. 574143

Article Info

Article history:

Manuscript ID:

IJPHI3115192024
Received: 31- June -2024
Revised :15-june-2024
Accepted: 19-june-2024
Available online: June 2024

Keywords:
COVID-19, kinase inhibitors, antiviral therapy, immunomodulation, SARS-CoV-2.

Corresponding Author:

Email

ramdas21@gmail.com

Abstract

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has posed significant global challenges, impacting millions and straining healthcare systems. With over 600 million confirmed cases worldwide and a death rate of approximately 1% as of May 2024, there is an urgent need for effective treatments. Kinase inhibitors, traditionally used in cancer therapy, have emerged as promising candidates due to their multifaceted antiviral and immunomodulatory properties. By targeting key signaling pathways involved in viral replication, host immune response modulation, and inflammatory cascades, these inhibitors offer a comprehensive approach to combating SARS-CoV-2 infection. This review explores the intricate mechanisms of action of kinase inhibitors, highlighting their antiviral potential, immunomodulatory effects, and synergistic interactions with existing treatments. We synthesize data from in vitro experiments, animal models, and clinical trials to provide a thorough understanding of the therapeutic landscape of kinase inhibitors in COVID-19. Notably, the FDA has approved Baricitinib in combination with remdesivir for hospitalized COVID-19 patients, demonstrating improved clinical outcomes and reduced recovery time. Other kinase inhibitors, such as Imatinib and Ruxolitinib, are undergoing clinical trials to assess their efficacy. Despite challenges, the repurposing of kinase inhibitors represents a viable strategy to mitigate the impact of COVID-19 and enhance patient outcomes.

INTRODUCTION:

COVID-19 is a global pandemic caused by the SARS-CoV-2 virus has created issues worldwide, affecting millions of people and straining healthcare systems [1]. There are over 600 million confirmed cases worldwide and a fatality rate of around 1% as of May 2024. The search for effective medicines has made researchers to investigate repurposing existing pharmaceuticals, with kinase inhibitors appearing as a promising class of drugs [2]. These inhibitors, which have historically been employed in cancer therapy, have various antiviral and immunomodulatory effects that make them promising drugs to fight against COVID-19. Kinase inhibitors provide a holistic approach to dealing with SARS-CoV-2 infection by targeting critical signaling pathways involved in viral replication, host immune response modulation, and inflammatory cascades [3].

Kinase inhibitors include various well-known drugs like imatinib, ruxolitinib, baricitinib, and tofacitinib [4], as well as newer drugs like sunitinib, dasatinib, and sorafenib, which have shown promise in preclinical studies for their ability to interfere with viral pathogenesis at various stages. These inhibitors disrupt viral internalization, inhibit replication of the genetic material, and prevent the cell-to-cell signal transduction. They also exhibit immunomodulatory effects to migitate the excessive inflammatory response showcasing their diverse strategies in combating COVID-19 [4,5].

This review explores the mechanisms of kinase inhibitors in treating COVID-19, focusing on their antiviral and immunomodulatory effects, and their potential synergy with existing treatments. By synthesizing data from in vitro studies, animal models, and clinical trials, it aims to provide a comprehensive understanding of their therapeutic potential. Promising results are emerging from ongoing clinical trials, including the FDA-approved use of baricitinib with remdesivir, and the evaluation of other inhibitors like imatinib and ruxolitinib for safety and efficacy in COVID-19 treatment.

KINASE INHIBITORS AS POSSIBLE ANTIVIRAL AGENTS IN COVID-19

Kinase inhibitors have emerged as promising antiviral agents against SARS-CoV-2, the virus responsible for COVID-19. These inhibitors target specific cellular signaling pathways crucial for the viral lifecycle, offering a multifaceted approach to combating the virus [6].

The initial step in SARS-CoV-2 infection involves the attachment of the viral spike proteins to the ACE2 receptor of the host cell, facilitating viral internalization [7]. Kinase inhibitors like AXL inhibitors (e.g., gilteritinib, cabozantinib) [8]and NAK inhibitors (e.g., imatinib, ruxolitinib, sunitinib) can disrupt this attachment process [9]. AXL inhibitors interfere with the binding of the viral spike

proteins to the ACE2 receptor, while NAK inhibitors target the clathrin-mediated endocytosis pathway used by the virus for cellular entry [10].

Once inside the host cell, SARS-CoV-2 hijacks the cellular machinery to replicate its genetic material and synthesize viral proteins. This replication process depends on various cellular signaling pathways, including mTOR-PI3K-AKT, ABL-BCR/MAPK, and DNA damage response (DDR) pathways [11]. Kinase inhibitors targeting these pathways, such as mTOR-PI3K-AKT inhibitors (e.g., vistusertib, everolimus) [12], ABL-BCR/MAPK inhibitors (e.g., nilotinib, bosutinib) [13], and DDR inhibitors (e.g., berzosertib, olaparib) [14], have demonstrated the ability to stop the viral replication. By disrupting this essential signaling pathway, kinase inhibitors alter the ability of the virus to replicate and spread within the host cell.

During the assembly phase of the viral lifecycle, newly synthesized viral components are packaged into mature virus particles [15]. Kinase inhibitors that interfere with translation, membrane trafficking, and stress response pathways may disrupt the assembly of infectious viral particles. By precisely targeting these cellular processes, kinase inhibitors have the potential to inhibit the assembly and release of mature virus particles, thereby diminishing viral infectivity and transmission [16,17].

The mature virus particles that are released from the host cell represent a critical stage in the viral lifecycle that kinase inhibitors can also target [18]. JAK inhibitors (e.g., baricitinib, tofacitinib) [19] and BTK inhibitors (e.g., acalabrutinib, zanubrutinib) [20] have shown the potential to modulate signaling pathways involved in this process and impede the virus ability to exit the host cell and infect neighboring cells.

The repurposing of FDA-approved kinase inhibitors for COVID-19 treatment offers several advantages, including established safety profiles and availability for clinical use. Many kinase inhibitors, such as imatinib, ruxolitinib, baricitinib, tofacitinib, and silmitasertib, are currently undergoing clinical trials to assess their efficacy against SARS-CoV-2. Combining kinase inhibitors with other therapies may enhance their therapeutic potential [21].

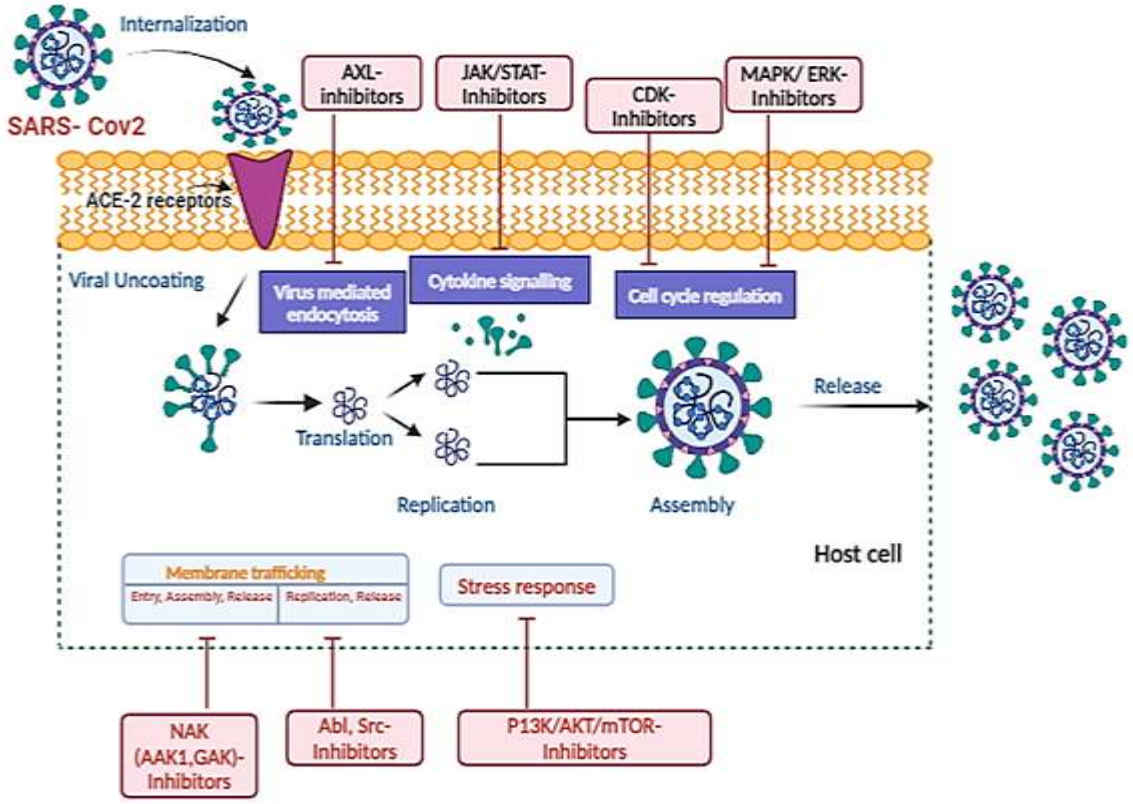

Fig. 1: Mechanism of PKI as an antiviral agent in Covid-19

KINASE INHIBITORS AS POSSIBLE IMMUNOMODULATORY AGENTS IN COVID-19

Kinase inhibitors have become crucial in the fight against COVID-19, particularly for their role as immunomodulators targeting the cytokine storm [22]. The cytokine storm, marked by the excessive release of pro-inflammatory cytokines like IL-2, IL-6, IL-8, and TNF-α, significantly contributes to severe COVID-19 complications such as acute lung injury and ARDS. These inhibitors work by blocking specific kinases, disrupting viral replication, and aiding COVID-19 management [23]. They interfere with cytokine signaling pathways and immune effector pathways, potentially reducing the risk of cytokine storms and associated tissue damage, which is vital in preventing multiorgan failure and death in severe cases [24]. Prominent kinase inhibitors include Baricitinib, a JAK inhibitor approved for use with remdesivir, Imatinib, a tyrosine kinase inhibitor under investigation, and Ruxolitinib, another JAK inhibitor being explored for managing hyperinflammation. Silmitasertib and Tofacitinib are also being studied for their roles in COVID-19-related inflammation [25][26].

JAK inhibitors like baricitinib have shown to improve severe pneumonia and reduce mortality by regulating cytokine signals such as IL-6, IL-12, IFN-γ, and GM-CSF, reducing JAK-dependent cytokine storms [26]. These

inhibitors target cytokine signaling, immune effector pathways, and inflammation, decreasing the production of pro-inflammatory cytokines and inhibiting immune cell activation [22][27]. Clinical trials are ongoing to evaluate the effectiveness and safety of kinase inhibitors in managing the cytokine storm in severe COVID-19, aiming to reduce inflammation and improve patient outcomes [28][29]. Besides COVID-19, kinase inhibitors are promising in cancer treatment by targeting kinases involved in cell growth, proliferation, and survival. The repurposing of kinase inhibitors from cancer treatment to COVID-19 management underscores their potential to modulate key signaling pathways in multiple diseases [29][30]. Continued research is essential to optimize the use of kinase inhibitors in COVID-19 therapy.

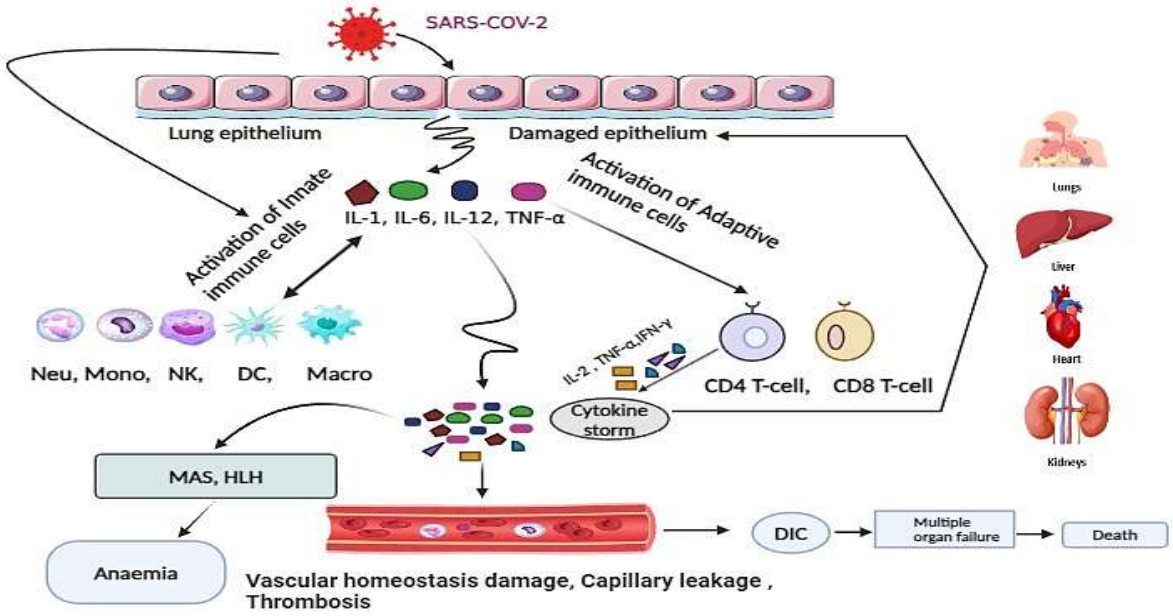

Fig. 2: Mechanism of formation of Cytokine storm and its complications.

PRECLINICAL AND CLINICAL EVIDENCE OF KINASE INHIBITORS IN COVID-19 TREATMENT

Kinase inhibitors have emerged as potential therapeutic agents in the fight against COVID-19. These inhibitors, including Imatinib, Ruxolitinib, Silmitasertib, and Tofacitinib, show promise in targeting virus-associated proteins and symptoms like pneumonia, fibrosis, and inflammation [26]. By disrupting the virus's life cycle and modulating the immune response, they offer a multifaceted approach to combating COVID-19. Baricitinib, a Janus kinase (JAK) inhibitor, has received FDA approval for use with Remdesivir for

hospitalized COVID-19 patients. JAK inhibitors like Baricitinib demonstrate dual anti-viral and anti-inflammatory properties, making them attractive for repurposing in COVID-19 treatment. They can mitigate the hyperinflammatory response in severe cases, improving patient outcomes [19,21,26].

Clinical trials have shown that JAK inhibitors can reduce mortality rates, enhance clinical recovery, shorten recovery time, and decrease the need for invasive mechanical ventilation in hospitalized patients. These inhibitors are associated with a lower risk of serious adverse events, highlighting their potential as safe and effective treatment options [31]. Kinase inhibitors, particularly JAK inhibitors, are being investigated for targeting cytokine storms and inflammation in COVID-19 pneumonia. By modulating the immune response and reducing excessive inflammation, these inhibitors can improve outcomes for patients with severe pneumonia. The repurposing of existing kinase inhibitors leverages their established safety profiles and mechanisms of action, potentially expediting effective therapies [32]. The versatility of kinase inhibitors in targeting various aspects of COVID-19 pathogenesis underscores their potential as valuable treatment additions. Continued research and clinical trials are essential to further understand their efficacy, safety, and optimal use in managing COVID-19.

CHALLENGES OF USING KINASE INHIBITORS FOR COVID-19 TREATMENT

When considering kinase inhibitors for COVID-19 treatment, several challenges need to be addressed [21]. Current investigations rely heavily on preclinical studies and anecdotal data, requiring rigorous, large-scale clinical trials for robust evidence [33,34]. Kinase inhibitors approved for malignancies may increase infection risk in COVID-19 patients, necessitating careful consideration of safety profiles and drug interactions [35,36]. Their pharmacokinetic properties present challenges, as some require long-term dosing and may not optimally target affected organs like the lungs [37,38].

Combining kinase inhibitors with antivirals and IL-6 blocking agents shows promise, but issues with drug interactions, safety, and dosing must be addressed. Selecting inhibitors with favorable pharmacokinetic profiles for safe co-administration is crucial [39,40]. The diverse disease severity and comorbidities among COVID-19 patients necessitate tailored treatments to optimize outcomes.

Despite these challenges, kinase inhibitors have potential benefits in targeting the viral life cycle and inflammatory response, making them promising for COVID-19 treatment. Continued research and clinical trials are essential to overcome these challenges and determine the most effective use of kinase inhibitors in managing COVID-19.

FUTURE DIRECTIONS OF USING KINASE INHIBITORS FOR COVID-19 TREATMENT

The future directions of using kinase inhibitors for COVID-19 treatment involve several key

aspects that are crucial for advancing this therapeutic approach. Repurposing FDA-approved kinase inhibitors shows promise in combating COVID-19 by targeting the viral life cycle and the inflammatory response associated with the disease. This approach aims to reduce viral propagation and alleviate severe symptoms.

Combining kinase inhibitors with other therapies, such as antivirals or targeted treatments, has demonstrated potential in clinical trials for COVID-19. This combined strategy enhances efficacy against the virus and its complications, providing a more comprehensive treatment approach. Exploring novel options like combination therapy and targeting specific proteins linked to the virus or lung health could yield positive outcomes in managing COVID-19 infections.

Additionally, investigating the JAK-STAT signaling system, which contributes to hyper-immune activation in COVID-19 patients, offers a promising avenue for future research. Repurposing FDA-approved and experimental drugs that target this pathway may help in mitigating the inflammatory response seen in severe COVID-19 cases, potentially preventing conditions like acute respiratory distress syndrome (ARDS) and multiple organ failure.

CONCLUSION

Repurposing kinase inhibitors presents a promising strategy for combating COVID-19 by targeting viral replication, modulating immune responses, and reducing inflammation. Despite the potential benefits, challenges such as understanding the precise mechanisms, managing side effects, and ensuring long-term safety remain. Ongoing research and clinical trials continue to explore the potential of these inhibitors, offering hope for advancements in therapy. Combining kinase inhibitors with other treatments and tailoring strategies to individual patient needs may significantly improve outcomes in the fight against COVID-19. However, more clinical trials are necessary to evaluate their long-term efficacy and safety. Additionally, there is a need to investigate combination therapies and explore newer, more selective kinase inhibitors. Future research should focus on better understanding the mechanisms of action and optimizing the therapeutic use of these inhibitors in viral infections.

Conflict of Interest: None.

Financial support: None.

Ethical statement: None.

REFERENCES:

1. Filip R, Gheorghita Puscaselu R, Anchidin-Norocel L, Dimian M, Savage WK. Global challenges to public health care systems during the COVID-19 pandemic: a review of pandemic measures and problems. J Pers Med. 2022;12(8):1295.
2. Xue Y, Mei H, Chen Y, Griffin JD, Liu Q, Weisberg E, et al. Repurposing clinically available drugs and therapies for pathogenic targets to combat SARS-CoV-2. MedComm. 2023;4(3):e254.
3. Velásquez PA, Hernandez J, Galeano E, Hincapié-García J, Rugeles M, Zapata-Builes W. Effectiveness of drug repurposing and natural products against

SARS-CoV-2: a comprehensive review. Clin Pharmacol Adv Appl. 2024;16:1-25.

4. Cohen P, Cross D, Jänne PA. Kinase drug discovery 20 years after imatinib: progress and future directions. Nat Rev Drug Discov. 2021;20(7):551-69.
5. Naik RR, Shakya AK, Aladwan SM, El-Tanani M. Kinase inhibitors as potential therapeutic agents in the treatment of COVID-19. Front Pharmacol. 2022;13:1-12.
6. Malekinejad Z, Baghbanzadeh A, Nakhlband A, Baradaran B, Jafari S, Bagheri Y, et al. Recent clinical findings on the role of kinase inhibitors in COVID-19 management. Life Sci. 2022;306:120809.
7. Le K, Kannappan S, Kim T, Lee JH, Lee HR, Kim KK. Structural understanding of SARS-CoV-2 virus entry to host cells. Front Mol Biosci. 2023;10:1288686.
8. Fernandez S, Desplat V, Villacreces A, Guitart AV, Milpied N, Pigneux A, et al. Targeting tyrosine kinases in acute myeloid leukemia: why, who and how? Int J Mol Sci. 2019;20(14):3429.
9. Westerdijk K, Desar IME, Steeghs N, van der Graaf WTA, van Erp NP. Imatinib, sunitinib, and pazopanib: from flat-fixed dosing towards a pharmacokinetically guided personalized dose. Br J Clin Pharmacol. 2020;86(2):258-73.
10. Boytz R, Słabicki M, Ramaswamy S, Patten JJ, Zou C, Meng C, et al. Anti-SARS-CoV-2 activity of targeted kinase inhibitors: repurposing clinically available drugs for COVID-19 therapy. J Med Virol. 2022;95(1):e28157.
11. Garcia G, Sharma A, Ramaiah A, Sen C, Purkayastha A, Kohn DB, et al. Antiviral drug screen identifies DNA-damage response inhibitor as potent blocker of SARS-CoV-2 replication. Cell Rep. 2021;35(1):108940.
12. Aneva IY, Kashani HRK, Habtemariam S, Banach M, Sil PC, Sarkar K, et al. Can we use mTOR inhibitors for COVID-19 therapy? Comb Chem High Throughput Screen. 2022;25(11):1805-8.
13. Galimberti S, Baldini C, Baratè C, Ricci F, Balducci S, Grassi S, et al. The CoV-2 outbreak: how hematologists could help to fight COVID-19. Pharmacol Res. 2020;157:104866.
14. Grand RJ. SARS-CoV-2 and the DNA damage response. J Gen Virol. 2023;104(11):001918.
15. Mahajan S, Choudhary S, Kumar P, Tomar S. Antiviral strategies targeting host factors and mechanisms obliging+ ssRNA viral pathogens. Bioorg Med Chem. 2021;46:116356.
16. Hajjo R, Sabbah DA, Abusara OH, Kharmah R, Bardaweel S. Targeting human proteins for antiviral drug discovery and repurposing efforts: a focus on protein kinases. Viruses. 2023;15(2):568.
17. Dey S, Mondal A. Unveiling the role of host kinases at different steps of influenza A virus life cycle. J Virol. 2024;98(1):e01192-23.
18. Robinson M, Schor S, Barouch-Bentov R, Einav S. Viral journeys on the intracellular highways. Cell Mol Life Sci. 2018;75(20):3693-714.

19. Dupuis D, Fritz K, Ike E, Arogundade O, Adewara EO, Monday EO, et al. Current use of baricitinib in COVID-19 treatment and its future: an updated literature review. Cureus. 2022;14(9):e28680.
20. Kifle ZD. Bruton tyrosine kinase inhibitors as potential therapeutic agents for COVID-19: a review. Metab Open. 2021;11:100116.
21. Weisberg E, Parent A, Yang PL, Sattler M, Liu Q, Liu Q, et al. Repurposing of kinase inhibitors for treatment of COVID-19. Pharm Res. 2020;37(9):167.
22. Yang L, Xie X, Tu Z, Fu J, Xu D, Zhou Y. The signal pathways and treatment of cytokine storm in COVID-19. Signal Transduct Target Ther. 2021;6(1):255.
23. Nazerian Y, Ghasemi M, Yassaghi Y, Nazerian A, Hashemi SM. Role of SARS-CoV-2-induced cytokine storm in multi-organ failure: molecular pathways and potential therapeutic options. Int Immunopharmacol. 2022;113:109428.
24. Mohammed MA. Fighting cytokine storm and immunomodulatory deficiency: by using natural products therapy up to now. Front Pharmacol. 2023;14:1111329.
25. Sinha A, Deshwal H, Vashisht R. Safe and effective use of baricitinib and remdesivir in hospitalized patients with coronavirus (COVID-19). PubMed; 2024. Available from: https://pubmed.ncbi.nlm.nih.gov/36943958.
26. Pillaiyar T, Laufer S. Kinases as potential therapeutic targets for anti-coronaviral therapy. J Med Chem. 2021;65(2):955-82.
27. Zarrin AA, Bao K, Lupardus P, Vucic D. Kinase inhibition in autoimmunity and inflammation. Nat Rev Drug Discov. 2021;20(1):39-63.
28. Quirch M, Lee J, Rehman S. Hazards of the cytokine storm and cytokine-targeted therapy in patients with COVID-19: review. J Med Internet Res. 2020;22(8):e20193.
29. Zheng W, Zeng Z, Lin S, Hou P. Revisiting potential value of antitumor drugs in the treatment of COVID-19. Cell Biosci. 2022;12(1):165.
30. Chandrasekaran B, Saravanan M. Editorial: pharmacological and biochemical perspectives of kinase inhibitors in cancer and COVID-19 therapeutics. Front Pharmacol. 2023 Jun 6;14:1229673.
31. Zhang X, Shang L, Fan G, Gu X, Xu J, Wang Y, et al. The efficacy and safety of Janus kinase inhibitors for patients with COVID-19: a living systematic review and meta-analysis. Front Med. 2022;8:800492.
32. Tanaka Y. A review of Janus kinase inhibitors for the treatment of COVID-19 pneumonia. Inflamm Regen. 2023;43(1):3.
33. Quartermaine C, Ghazi SM, Yasin A, Awan FT, Fradley M, Wiczer T, et al. Cardiovascular toxicities of BTK inhibitors in chronic lymphocytic leukemia. JACC CardioOncol. 2023;5(5):570-90.
34. Duan XP, Qin BD, Jiao XD, Liu K, Wang Z, Zang YS. New clinical trial design in precision medicine: discovery, development and direction. Signal Transduct Target Ther. 2024;9(1):57.

35. Kumara Prasad SA, Krishna BN, Prarthan KN, Kavyashree S, Shabaraya AR. Synthesis, spectroscopic, and antibacterial studies of some N-phenylpyridinium chloride derivatives. J Community Pharm Pract. 2024;4(2):28-39.
36. Li G, Hilgenfeld R, Whitley R, De Clercq E. Therapeutic strategies for COVID-19: progress and lessons learned. Nat Rev Drug Discov. 2023 Jun;22(6):449-75.
37. Kabir ER, Mustafa N, Nausheen N, Sharif Siam MK, Syed EU. Exploring existing drugs: proposing potential compounds in the treatment of COVID-19. Heliyon. 2021;7(2):e06284.
38. Bhat R, Gopikrishna, Krishna N, Prarthan, Pradeep S, Shetty S, Kavyashree, Shabaraya R. Phytochemical constituent and anti-bacterial activity of Tabernaemontana divaricata (Dwarf) leaves. J Biochem Technol. 2024;15(1):46-51.
39. Krishna NB, Gopikrishna UV, Prarthan KN, Pradeep PS, Shetty S, Kavyashree S, Shabaraya AR. Formulation and evaluation of herbal facepack for healthy skincare. Int J Curr Res Physiol Pharmacol. 2024;8(1):10-24.
40. García-Cárceles J, Caballero E, Gil C, Martínez A. Kinase inhibitors as underexplored antiviral agents. J Med Chem. 2021;65(2):935-54.