Commentary

[Perspective] Hypochlorous Acid (HOCL): A Multifaceted and Promising Therapeutic Perspective Against Human Immunodeficiency Virus (HIV)

Maher M. Akl[1], Amr Ahmed[2]

1. Department of Chemistry, Faculty of Science, Mansoura University, Egypt; 2. Ministry of Health Saudi Arabia, Riyadh, Saudi Arabia

Human Immunodeficiency Virus (HIV) infection, known as Acquired Immunodeficiency Syndrome (AIDS), continues to be a major global health issue, impacting millions worldwide. The disease progresses through the depletion of CD4+ T lymphocytes, compromising the immune system's capacity to fight opportunistic infections and cancers, leading to high morbidity and mortality without treatment. The socioeconomic impact of HIV/AIDS is profound, exacerbating poverty and inequality, especially in under-resourced regions. Standard HIV/AIDS management includes antiretroviral therapy (ART), prophylaxis against opportunistic infections, and supportive care, with ART regimens comprising various drug classes such as nucleoside and non-nucleoside reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, and entry inhibitors. These therapies have transformed HIV into a manageable chronic condition, yet access to these treatments remains unequal globally. This perspective traditional approaches to HIV therapy, the socioeconomic impacts of the disease, and the potential of innovative treatments like hypochlorous acid (HOCl). HOCl is a naturally occurring antimicrobial agent produced by neutrophils, effective against a broad spectrum of pathogens through mechanisms of oxidative damage and immune modulation. Given its antiviral properties, especially in the context of early innate immune responses, this review explores the feasibility of HOCl as a novel therapeutic avenue in HIV/AIDS management, aiming to broaden the current treatment landscape and address ongoing challenges in global HIV care.

Corresponding author: Maher M. Akl, maherakl555@gmail.com

 doi.org/10.32388/27FKRB

1. *Introduction*

Human Immunodeficiency Virus (HIV) infection, commonly known as Acquired Immunodeficiency Syndrome (AIDS), remains a significant global health challenge, posing multifaceted threats to individuals and societies alike. Characterized by the progressive depletion of CD4+ T lymphocytes, the virus undermines the immune system's ability to combat opportunistic infections and malignancies, leading to severe morbidity and mortality if left untreated [1]. The gravity of HIV/AIDS lies not only in its direct health implications but also in its broader socio-economic ramifications, perpetuating cycles of poverty and inequality, particularly in resource-limited settings. Traditional therapeutic approaches for HIV/AIDS management encompass a combination of antiretroviral therapy (ART), opportunistic infection prophylaxis, and supportive care interventions [2]. Antiretroviral drugs target various stages of the viral lifecycle, including entry, reverse transcription, integration, and maturation, thereby suppressing viral replication and mitigating immune system deterioration. The standard ART regimens typically consist of a combination of nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), and entry inhibitors, tailored to optimize virological efficacy and minimize drug resistance emergence [3]. In addition to pharmacological interventions, adjunctive measures such as prophylactic antibiotics, antifungals, and vaccinations play pivotal roles in preventing and managing opportunistic infections commonly associated with HIV/AIDS, including Pneumocystis jirovecii pneumonia, Mycobacterium avium complex disease, and cytomegalovirus retinitis. Furthermore, nutritional supplementation, psychological support, and adherence counseling are integral components of comprehensive HIV care, addressing the multifaceted needs of patients and enhancing treatment outcomes [4]. Despite significant advancements in HIV/AIDS therapeutics, challenges persist in ensuring universal access to care, particularly in resource-constrained settings characterized by limited healthcare infrastructure and financial constraints. Disparities in treatment access, stigma, and discrimination continue to hinder effective disease management and exacerbate the burden of HIV/AIDS on vulnerable populations, underscoring the imperative for sustained global solidarity and concerted efforts to combat the epidemic comprehensively [5]. Hypochlorous acid (HOCl) is a crucial component of the innate immune system, synthesized endogenously within neutrophils and other phagocytic cells through the enzymatic action of myeloperoxidase (MPO) on chloride ions (Cl-) and hydrogen peroxide (H2O2).

This enzymatic reaction results in the formation of hypochlorous acid, a potent oxidizing agent known for its broad-spectrum antimicrobial activity against bacteria, viruses, and fungi. The chemical mechanism underlying the antimicrobial action of hypochlorous acid involves its ability to disrupt essential cellular structures and metabolic pathways through oxidative damage. Upon contact with microbial pathogens, HOCl readily penetrates the cell membranes, where it oxidizes critical biomolecules such as lipids, proteins, and nucleic acids. This oxidative stress leads to membrane destabilization, protein denaturation, and DNA/RNA damage, ultimately compromising microbial viability and inhibiting replication [6][7].

Furthermore, hypochlorous acid exhibits selective reactivity towards specific molecular targets within microbial cells, including thiol groups (-SH) present in cysteine residues of proteins. By oxidizing these thiol groups, HOCl disrupts essential enzymatic activities and structural integrity, impeding microbial growth and proliferation. Additionally, hypochlorous acid can modulate the redox balance within microbial cells, leading to the generation of reactive oxygen species (ROS) and subsequent oxidative stress-induced cell death. In the context of viral infections, hypochlorous acid exerts its antiviral effects by targeting the viral envelope, which comprises lipid bilayers and glycoproteins essential for viral entry and fusion with host cells. HOCl disrupts the lipid envelope's integrity, destabilizing viral particles and preventing their attachment to host cell receptors. Moreover, hypochlorous acid can oxidize viral proteins and nucleic acids, inhibiting viral replication and assembly [8]. The immunomodulatory properties of hypochlorous acid extend beyond its direct antimicrobial effects, as it also facilitates immune cell activation and cytokine signaling to enhance host defense mechanisms. Neutrophils release hypochlorous acid into the extracellular environment during the respiratory burst, creating a localized microenvironment conducive to pathogen clearance and tissue repair. Additionally, hypochlorous acid promotes the recruitment and activation of other immune cells, such as macrophages and dendritic cells, to amplify the immune response and facilitate antigen presentation [9]. In this perspective, we delve into the feasibility of harnessing a drug derived from hypochlorous acid as a promising antiviral agent against Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome (AIDS). The exploration of hypochlorous acid as a potential therapeutic intervention for HIV/AIDS is based on its well-established antimicrobial properties, including its ability to target a broad spectrum of pathogens through oxidative damage and modulation of the immune response. Given the urgent need for novel antiviral therapies and the

multifaceted nature of HIV infection, investigating the potential utility of hypochlorous acid derivatives holds promise for expanding the armamentarium of HIV/AIDS treatment options.

2. *Subversion of Early Innate Immune Responses by HIV: Mechanisms and Implications for Pathogenesis*

Human Immunodeficiency Virus (HIV) represents a formidable challenge to the host's innate immune system, intricately evading and subverting early defense mechanisms essential for viral containment. At the forefront of this battle, the innate immune response, characterized by its rapid and nonspecific nature, serves as the initial line of defense against invading pathogens. However, HIV has developed sophisticated strategies to exploit vulnerabilities within this innate immune armor, perpetuating its pathogenicity and persistence within the host. Central to HIV's subversion of the innate immune response is its adept manipulation of host cell receptors and signaling pathways. By specifically targeting CD4+ T lymphocytes and macrophages, pivotal components of innate immunity, HIV gains entry into host cells through interactions with CD4 receptors and co-receptors like CCR5 or CXCR4. This infiltration not only facilitates viral replication but also disrupts normal immune cell function, crippling the host's ability to mount an effective antiviral defense [10].

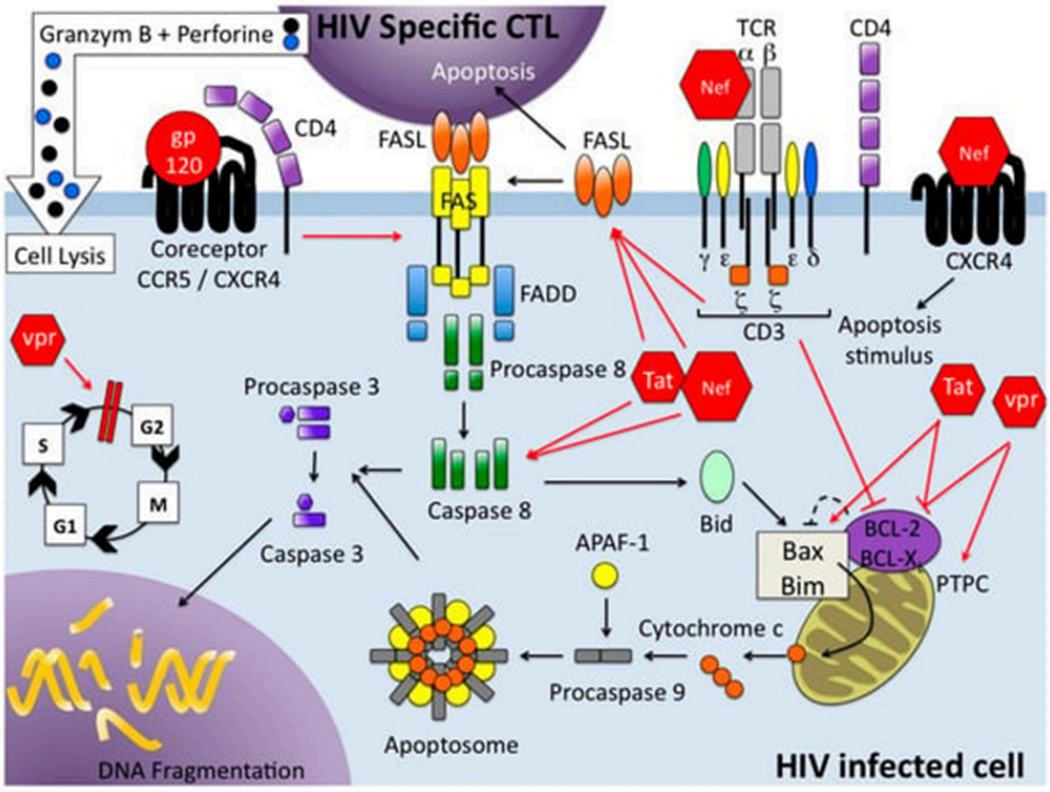

Figure 1. illustrates the apoptosis pathways in HIV-infected helper T cells, detailing both the extrinsic (death receptor-mediated) and intrinsic (mitochondrial-mediated) mechanisms. Key HIV proteins involved in the apoptosis of CD4+ T cells include the envelope glycoprotein gp120, the negative regulatory factor Nef, the transactivator of transcription Tat, and the viral protein R (Vpr), all highlighted in red. The envelope glycoprotein gp120 binds to the CD4 receptor on helper T cells and utilizes either the CCR5 or CXCR4 chemokine receptors as coreceptors to facilitate viral entry. This interaction also results in an upregulation of Fas ligand (FASL) on the surface of these cells, contributing to the activation of the extrinsic apoptosis pathway. Furthermore, the soluble Nef protein directly engages with the CXCR4 receptor to promote apoptotic signaling. Nef's role extends to interacting with the T cell receptor (TCR)-CD3 complex, enhancing the expression of Fas and FasL on the cell surface, while concurrently suppressing the anti-apoptotic proteins of the Bcl-2 family. In parallel, the Tat protein enhances the Fas/FasL pathway and activates caspase 8, further propagating the apoptotic signal. Both Tat and Vpr proteins contribute to mitochondrial dysfunction by inhibiting Bcl-2 family proteins, which leads to cytochrome c release, apoptosome formation, and subsequent apoptosis. Additionally, HIV-1 Vpr has been found to arrest cells in the G2 phase of the cell cycle, thereby influencing cell survival. This figure encapsulates the complex interplay of viral proteins and cellular receptors that orchestrate the demise of infected T cells, highlighting potential targets for therapeutic intervention in HIV treatment. Key terms included

doi.org/10.32388/27FKRB

are T cell receptor (TCR), cytotoxic T lymphocyte (CTL), Fas ligand (FasL), Fas-associated death domain (FADD), cysteinyl aspartic acid-protease (caspase), B-cell lymphoma protein 2 (BCL-2), BCL-2 like 1 (BCL-X), BCL2 associated X protein (Bax), apoptotic protease activating factor (APAF), and permeability transition pore complex (PTPC).

Source: [11]

In addition to hijacking host cell machinery, HIV strategically evades detection by pattern recognition receptors (PRRs), which serve as sentinels for detecting viral invaders. Through intricate structural and functional adaptations, HIV eludes recognition by Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), and other PRRs, thereby thwarting activation of innate immune signaling pathways and dampening the production of crucial antiviral cytokines. Moreover, HIV orchestrates a multifaceted assault on innate immune effector cells, including natural killer (NK) cells and dendritic cells (DCs), further undermining early antiviral defenses. By depleting CD4+ T cells and disrupting lymphoid tissue architecture, HIV perpetuates a state of chronic immune activation and inflammation, fostering an environment conducive to viral replication and immune evasion [12].

3. *The Role of Hypochlorous Acid in Early Innate Immune Response and HIV Inhibition*

Hypochlorous acid (HOCl), a naturally occurring component of the innate immune system, plays an instrumental role in host defense mechanisms against microbial threats, including HIV. Generated by neutrophils during the respiratory burst, HOCl exhibits potent antimicrobial properties that disrupt the structural integrity and viability of pathogens through a variety of mechanisms [13].

HOCl's primary mode of action involves oxidative damage to essential biomolecules. It selectively targets lipids, proteins, and nucleic acids within microbial cells and viral particles. This oxidative damage results in the disruption of cellular membranes and the denaturation of viral proteins, which are crucial for viral attachment, entry, and replication. For instance, HOCl-induced oxidation of viral envelope proteins impairs the ability of viruses like HIV to fuse with host cell membranes, effectively blocking entry into the host cells. In addition to direct oxidative damage, HOCl exerts further antiviral effects by targeting specific thiol groups (-SH) found in cysteine residues within viral proteins. These

thiol groups are critical for the proper folding and function of viral enzymes and structural proteins. Oxidation of these thiol groups by HOCl leads to misfolding and inactivation of viral proteins, thereby impeding viral replication processes and assembly. Moreover, HOCl enhances the immune response through its immunomodulatory properties. It activates immune cells, such as macrophages and neutrophils, boosting their phagocytic and bactericidal activities. HOCl also promotes the production of cytokines, which play a pivotal role in mediating and regulating the immune response. This cytokine signaling enhances the recruitment and activation of additional immune cells to the site of infection, fostering a robust antiviral immune response. The multifaceted mechanisms by which HOCl operates make it a promising agent in the early-phase immune response against HIV infection. By leveraging its oxidative and immunomodulatory capabilities, interventions that harness HOCl could potentially mitigate HIV transmission and disease progression. Recognizing these mechanisms provides valuable insights into developing novel therapeutic strategies that utilize innate immune responses to combat viral infections effectively. Further exploration into the therapeutic potential of HOCl in HIV prevention and treatment is essential, offering hope for innovative solutions to this global health challenge [14][15][16].

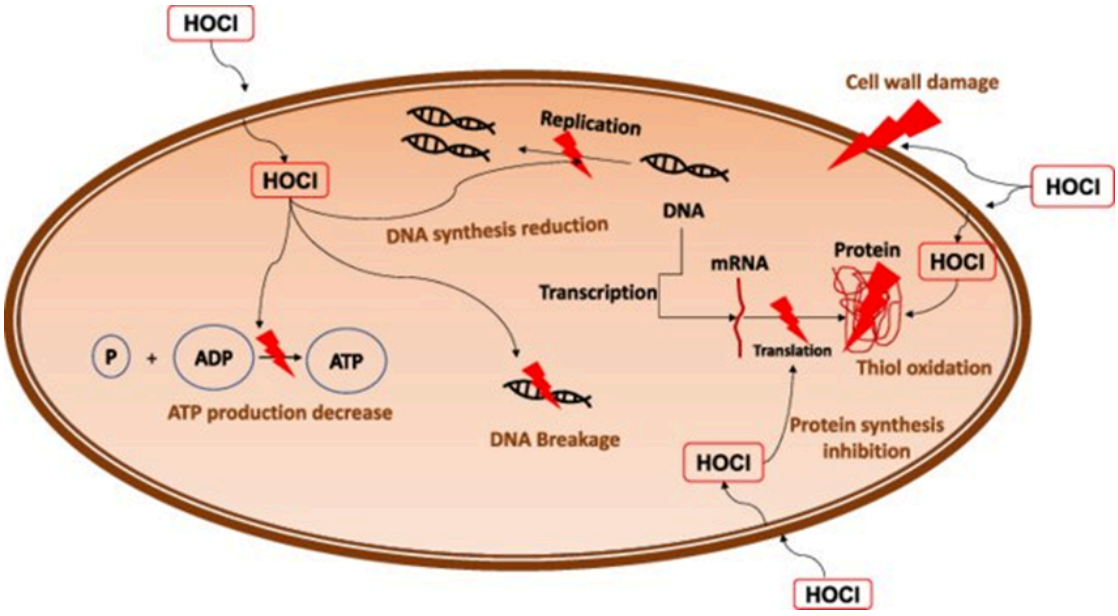

Figure 2. depicts the proposed mechanism of action of hypochlorous acid (HOCl) not only against bacterial cells but also potentially applicable to viral pathogens. HOCl, being uncharged, easily crosses the cell wall and membrane structures. Upon entry into the cell, HOCl disrupts critical cellular functions including DNA synthesis by inhibiting the replication processes. It also impairs protein synthesis, targeting thiol groups in proteins and enzymes essential for bacterial and possibly viral functionality. Further, HOCl depresses DNA replication and inhibits cell wall synthesis, effectively stunting bacterial growth. Its impact extends to the metabolic processes of the cell by reducing adenosine triphosphate (ATP) production, a vital energy source, thereby crippling the cell's energy metabolism. This schematic serves to illustrate the broad-spectrum antimicrobial properties of HOCl, emphasizing its potential utility in targeting a variety of microbial threats including both bacteria and viruses, thereby highlighting its relevance in antimicrobial strategies.

Source: [17]

Safety Profile of Hypochlorous Acid (HOCl)

Hypochlorous acid (HOCl) is renowned for its safety and efficacy as an antimicrobial agent, particularly in the context of its endogenous production by neutrophils as part of the human immune response. Its use in various clinical and environmental applications underlines its low toxicity and general safety for human exposure. HOCl operates primarily through the oxidation of microbial cell structures and biomolecules, a mechanism that is selective and does not pose significant risk to

human cells at therapeutic concentrations. This specificity is largely due to the transient nature of HOCl and its rapid decomposition in biological environments, which minimizes potential systemic toxicity. Furthermore, when applied topically or used in wound care, HOCl has shown minimal adverse effects, making it a favorable choice for managing infections and promoting healing [18].

Chemical Profile of Calcium Hypochlorite as an HOCl Source

Calcium hypochlorite, commonly utilized as a source of hypochlorous acid, is a chemical compound with the formula $Ca(OCl)_2$. It serves as a potent oxidizing agent and, upon dissolution in water, releases HOCl through a simple hydrolysis reaction; This reaction results in the formation of hypochlorous acid along with calcium hydroxide as a byproduct. The availability of HOCl from calcium hypochlorite is advantageous, especially in scenarios requiring large-scale disinfection or where direct handling and storage of concentrated HOCl may be impractical. Calcium hypochlorite's stability as a solid and its high oxidizing power also contribute to its extensive use in water treatment, sanitization, and as an antiviral and antibacterial agent [19].

Guidance on Dosing of Calcium Hypochlorite for Short-Term Use

For the experimental therapeutic use of calcium hypochlorite as a source of hypochlorous acid, particularly in research settings involving viral infections such as HIV, a cautious approach to dosing is essential. Based on the experimental context, a recommended dosage for a short-term study might involve administering calcium hypochlorite once daily for a duration of 7 days following a single injection at a dose of 75 mg/kg. This regimen is designed to investigate the potential therapeutic effects of HOCl in modulating immune responses or combating viral loads within a controlled setting. The specific concentration of calcium hypochlorite and the method of administration should be tailored to the experimental design, ensuring adequate safety and efficacy. Monitoring for any signs of toxicity or adverse effects during and after treatment is crucial to validate the safety and potential therapeutic benefits of this regimen [16].

4. Discussion

The exploration of hypochlorous acid (HOCl) as a potential antiviral agent in the context of HIV infection opens new avenues for addressing a persistent global health issue. HOCl, a naturally occurring component of the innate immune system's arsenal, is primarily synthesized by neutrophils

during the respiratory burst. Its broad-spectrum antimicrobial properties stem from its capacity to induce oxidative damage to essential biomolecules within pathogens, including lipids, proteins, and nucleic acids. This oxidative damage compromises the integrity of viral envelopes, impairs the function of viral proteins, and disrupts the replication process. In the case of HIV, the virus's reliance on specific protein structures and functions for entry and replication makes it a feasible target for HOCl's oxidative mechanisms. Moreover, the selective reactivity of HOCl towards thiol groups in cysteine residues disrupts critical enzymatic activities vital for viral replication. By altering the redox state of these thiol groups, HOCl not only hampers the proper folding and function of viral proteins but also impairs the overall viral assembly and maturation process. This detailed understanding of HOCl's action at the molecular level underscores its potential as a strategic tool in early-phase HIV infection management.

In addition to its direct antiviral effects, HOCl enhances the immune response by activating phagocytic cells and promoting cytokine signaling. This immunomodulatory role further supports the utility of HOCl in managing HIV, as it boosts host defenses, thereby potentially lowering viral load and transmission risk. However, the clinical application of HOCl in HIV therapy requires rigorous research to ensure efficacy, optimize delivery methods, and minimize potential side effects. Given the multifaceted nature of HIV pathogenesis and the challenges associated with current treatment modalities, the potential incorporation of HOCl into HIV management strategies presents a compelling case for extended research. Future studies should focus on the pharmacodynamics, safety profiles, and therapeutic windows of HOCl formulations to better integrate this innate immune molecule into the existing antiviral treatment landscape. Ultimately, the success of such interventions will depend on their ability to offer a significant improvement over current therapies, in terms of both efficacy and patient outcomes.

5. *Conclusion*

In conclusion, the strategic deployment of hypochlorous acid (HOCl) presents a compelling prospect for augmenting the therapeutic landscape against HIV/AIDS. As delineated in this perspective, HOCl harnesses potent antimicrobial properties that can be crucial for disrupting viral activities and enhancing immune responses. Particularly in the realm of HIV, where evasion and resistance to standard therapies pose significant challenges, HOCl offers a unique mechanism of action, targeting the virus and associated pathogens at multiple stages of their life cycles. This broad-spectrum

capability not only underscores the potential of HOCl as a therapeutic adjunct but also highlights the necessity for ongoing research to further elucidate its efficacy and safety in clinical contexts. By integrating advanced understanding of HOCl's mechanisms with innovative delivery systems and treatment protocols, it may become possible to significantly curtail HIV transmission and improve outcomes for those living with the disease. Thus, fostering a multidisciplinary approach to research and therapeutic application, we can hope to achieve a substantial impact on global HIV/AIDS management and patient quality of life.

Statements and Declarations

Funding information: The authors received no financial support for the research and publication of this article.

Competing interest declaration: The authors declare that there are no conflicts of interest.

References

1. ^*Kumah, E., Boakye, D. S., Boateng, R., & Agyei, E. (2023). Advancing the Global Fight Against HIV/Aids: Strategies, Barriers, and the Road to Eradication. Annals of global health, 89(1), 83. https://doi.org/10.5334/aogh.4277.*
2. ^*Zuma, T., Wight, D., Rochat, T., & Moshabela, M. (2017). Traditional health practitioners' management of HIV/AIDS in rural South Africa in the era of widespread antiretroviral therapy. Global health action, 10(1), 1352210. https://doi.org/10.1080/16549716.2017.1352210.*
3. ^*Aquaro, S., Borrajo, A., Pellegrino, M., & Svicher, V. (2020). Mechanisms underlying of antiretroviral drugs in different cellular reservoirs with a focus on macrophages. Virulence, 11(1), 400–413. https://doi.org/10.1080/21505594.2020.1760443.*
4. ^*Aberg, J., & Powderly, W. (2010). HIV: primary and secondary prophylaxis for opportunistic infections. BMJ clinical evidence, 2010, 0908.*
5. ^*Bouabida, K., Chaves, B. G., & Anane, E. (2023). Challenges and barriers to HIV care engagement and care cascade: viewpoint. Frontiers in reproductive health, 5, 1201087. https://doi.org/10.3389/frph.2023.1201087.*
6. ^*Ulfig, A., & Leichert, L. I. (2021). The effects of neutrophil-generated hypochlorous acid and other hypohalous acids on host and pathogens. Cellular and molecular life sciences: CMLS, 78(2), 385–414. https://*

doi.org/10.1007/s00018-020-03591-y.

7. ^*Mütze S, Hebling U, Stremmel W, Wang J, Arnhold J, Pantopoulos K, Mueller S. Myeloperoxidase-derived hypochlorous acid antagonizes the oxidative stress-mediated activation of iron regulatory protein 1. J Biol Chem. 2003 Oct 17;278(42):40542-9. doi: 10.1074/jbc.M307159200. Epub 2003 Jul 29. Erratum in: J Biol Chem. 2003 Dec 5;278(49):49662. PMID: 12888561.*
8. ^*Andrés, C. M. C., Pérez de la Lastra, J. M., Juan, C. A., Plou, F. J., & Pérez-Lebeña, E. (2022). Hypochlorous Acid Chemistry in Mammalian Cells-Influence on Infection and Role in Various Pathologies. International journal of molecular sciences, 23(18), 10735. https://doi.org/10.3390/ijms231810735.*
9. ^*Boecker, D., Zhang, Z., Breves, R., Herth, F., Kramer, A., & Bulitta, C. (2023). Antimicrobial efficacy, mode of action and in vivo use of hypochlorous acid (HOCl) for prevention or therapeutic support of infections. GMS hygiene and infection control, 18, Doc07. https://doi.org/10.3205/dgkh000433.*
10. ^*Guha, D., & Ayyavoo, V. (2013). Innate immune evasion strategies by human immunodeficiency virus type 1. ISRN AIDS, 2013, 954806. https://doi.org/10.1155/2013/954806.*
11. ^*Février, M.; Dorgham, K.; Rebollo, A. CD4+ T Cell Depletion in Human Immunodeficiency Virus (HIV) Infection: Role of Apoptosis. Viruses 2011, 3, 586-612. https://doi.org/10.3390/v3050586.*
12. ^*Masenga, S. K., Mweene, B. C., Luwaya, E., Muchaili, L., Chona, M., & Kirabo, A. (2023). HIV-Host Cell Interactions. Cells, 12(10), 1351. https://doi.org/10.3390/cells12101351.*
13. ^*Akl MM. Hypochlorous acid has emerged as a potential alternative to conventional antibiotics due to its broad-spectrum antimicrobial activity. Int J Clin Microbiol Biochem Technol. 2023; 6: 001-004. doi: 10.29328/journal.ijcmbt.1001026.*
14. ^*Ulfig, A., & Leichert, L. I. (2021). The effects of neutrophil-generated hypochlorous acid and other hypohalous acids on host and pathogens. Cellular and molecular life sciences: CMLS, 78(2), 385–414. https://doi.org/10.1007/s00018-020-03591-y.*
15. ^*Qadir Tantry, I., Ali, A., & Mahmood, R. (2021). Hypochlorous acid decreases antioxidant power, inhibits plasma membrane redox system and pathways of glucose metabolism in human red blood cells. Toxicology research, 10(2), 264–271. https://doi.org/10.1093/toxres/tfaa111.*
16. ^a, ^b*Akl MM, Nazmy EA, El-Khouly OA. Effect of calcium hypochlorite as a source of hypochlorous acid in ameliorating cyclophosphamide-induced pulmonary and cardiac injury in mice. Journal of Bioscience and Aplied Research. 2022; 8:212-220. doi: 10.21608/jbaar.2022.259963.*
17. ^*Kiamco, M.M., Zmuda, H.M., Mohamed, A. et al. Hypochlorous-Acid-Generating Electrochemical Scaffold for Treatment of Wound Biofilms. Sci Rep 9, 2683 (2019). https://doi.org/10.1038/s41598-019-3896*

8-y

18. ^*Block, M. S., & Rowan, B. G. (2020). Hypochlorous Acid: A Review. Journal of oral and maxillofacial surgery: official journal of the American Association of Oral and Maxillofacial Surgeons, 78(9), 1461–1466. https://doi.org/10.1016/j.joms.2020.06.029.*

19. ^*Rutala WA, Weber DJ. Disinfection, Sterilization, and Control of Hospital Waste. In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Elsevier Inc.; 2014. page 3294-3309.e1.*

Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.