JIMKI : JURNAL ILMIAH MAHASISWA KEDOKTERAN INDONESIA

ADVERTORIAL

e-ISSN : 2721-1924
ISSN : 2302-6391

KEUNTUNGAN DARI PENGGUNAAN PROSTRATIN DALAM MEMBALIKKAN LATENSI DAN ERADIKASI HUMAN IMMUNODEFICIENCY VIRUS

Pemanfaatan Ekstrak Tanaman Obat dalam Mengatasi Latensi dan Eradikasi HIV secara keseluruhan

Nadine Aurelie,[1]

Program Studi Pendidikan Dokter, Fakultas Kedokteran, Universitas Indonesia, Jakarta

ABSTRAK

Korespondensi:

Nadine Aurelie

Email Korespondensi:

nadine.aurelie@ui.ac.id

Riwayat Artikel

Diterima: 01 – 05 – 2022
Selesai revisi: 19 – 05 – 2022

DOI :

10.53366/jimki.v10i.520

Pendahuluan: Selama puluhan tahun, HIV telah menyebabkan dampak buruk kepada komunitas dengan kemunculan populasi rentan. Walaupun kondisi ini dapat distabilkan dengan penggunaan obat antiretroviral, muncul masalah lain seperti toksisitas dan resistensi obat akibat pemakaian jangka panjang. Oleh karena itu, para peneliti mencoba mengambil pendekatan berbeda dalam eradikasi infeksi HIV, yakni *shock and kill* dengan menggunakan *latency reversal agent*. Salah satu kandidat yang menjanjikan adalah prostratin, senyawa yang diperoleh dari ekstrak tanaman obat.
Pembahasan: Selain reaktivasi sel yang terinfeksi HIV dan berada dalam tahap laten, penggunaan prostratin dapat mempersiapkan sistem imun tubuh dalam eliminasi infeksi HIV, sehingga memperbesar kemungkinan kesembuhan seseorang. Kombinasi dengan obat-obat farmakologi lain juga dapat meningkatkan efektivitas sinergi dalam pendekatan *shock and kill*, sehingga mampu memaksimalisasi eradikasi infeksi HIV secara keseluruhan.
Simpulan: Oleh karena itu, berdasarkan pembahasan yang telah dipaparkan di atas, dapat disimpulkan bahwa penggunaan prostratin dapat memberikan beberapa keuntungan yang sebelumnya tidak didapatkan dari penggunaan agen pembalikkan latensi lain. Dengan demikian, penggunaan prostratin dapat membawa manusia lebih dekat untuk membasmi infeksi HIV secara total.

Kata Kunci: Agen pembalikkan latensi, HIV, Prostratin, Latensi, Syok dan pembunuhan

THE EDGE PROVIDED BY PROSTRATIN UTILIZATION IN REVERSING LATENCY AND ERADICATING HUMAN IMMUNODEFICIENCY VIRUS

The Application of Medicinal Plant Extract to Overcome Latency and Eradicate Human Immunodeficiency Virus Completely

ABSTRACT

Background: *For decades, HIV has caused severe impact toward society by generating vulnerable population. Even though this condition can be kept stabile with antiretroviral usage, other issues including toxicity and resistance emerge due to long term utilization. Therefore, researchers have taken new approach to eradicate HIV infection, which is through shock and kill pace using latency reversal agent. One of the promising candidates is prostratin, compound obtained from medicinal plant extract.*

Discussion: *Aside of reactivating latent HIV-infected cell, prostratin can also prepare related immune system function to combat and eliminate HIV infection, enhancing success chance to obtain full recovery. Combination alongside with other pharmacotherapy agents can further escalate synergist effectivity in shock and kill approach, thus maximizing eradication of HIV infection completely.*

Conclusion*: Therefore, based on the discussion that has been explained above, it can be sum up that prostratin has several advantages compared to other latency reversal agents. Thus, prostratin application might bring one step closer for mankind to annihilate HIV infection completely.*

Keywords: *HIV, Latency, Latency reversal agent, Prostratin, Shock and kill*

1. PENDAHULUAN

As one of the major burdens of society, Human Immunodeficiency Virus (HIV) has been a scourge in medical field. It was not until the discovery of antiretroviral therapy (ART) that the devastating progressive effect toward immune system could be suppressed into baseline. However, the sneaky method granted from reverse transcriptase enzyme allows HIV to integrate its genetic information to host cellular genome, providing temporary safe sanctuary from immune surveillance. In the right time when the host immune deescalates, the latent HIV will be reactivated once more and continue to cause havoc particularly toward one of the specific t cell subtypes, CD4+, until the host succumbs from severe opportunistic infection[1,2].

Theoretically, population infected by HIV can remain stabile as long as they take ART appropriately and treat the opportunistic infection accordingly. Nevertheless, the long-term medication arises new issue such as toxicity and drug

resistance, prompting the scientist to research and update medication line continuously. Therefore, alternative method must be discovered to tackle this endless issue. One of the proposed methods is latency reversal agent (LRA) obtained from nature, Prostratin[1,2].

2. PEMBAHASAN

One of the cunning moves made by HIV is to sneak its genetic information to host cellular genome, thus the hybrid gene, provirus, replicates coincidentally with normal cell replication cycle. Even though the viremia level can be kept in check through ART, HIV infection still persists nonetheless. Scientist starts to look for another alternative to eradicate HIV wholly. Scanning for window of opportunity, researcher tries to reverse latency state, providing vulnerable moment for HIV-infected cell to be targeted by host immune system or other pharmacotherapies that can annihilate HIV. This project is called shock and kill pace[1,2].

The agents that have been discovered to induce such effects are called LRA. As the technology advances, there have been long lists of LRA candidates that can be tested, each with different molecular intervening methods, pertaining complex method to unravel HIV latency. However, not all can achieve success when tested at in vivo subject. Researchers found out that the reason behind that ineffectiveness are caused by altered or weakened immune agents that play crucial roles in eliminating HIV such as natural killer cell in front line and CD8+ in adaptive response. For example, couple LRA candidates that inhibit HDAC such as Romidepsin and Panobinostat that influence immune function as well. The deficiency of CD8+ is also related to escape mutation where HIV-infected cells are not recognized, or in the state of dysfunctional/exhausted commonly found at chronic condition. Therefore, it is crucial to find the right selection of drug that can support immune defense at the same time. One of the listed candidates is Prostratin[1-4].

Prostratin is classified into Phorbol ester. This compound was initially found at poisonous plant native from New Zealand, *Pimela prostrata*. Then, this compound was also discovered at *Homalanthus nutans*, medicinal plant from Samoa. This plant is usually used by traditional healers to treat yellow fever symptom from viral hepatitis. Aside from activating latent HIV-infected cell, other study suggested that prostratin can also inhibit entry step of HIV replication cycle through CD4 and CXCR4 and CCR5 down-modulation, assisting further in HIV annihilation[2,5].

As a potent protein kinase C (PKC), prostratin can reactivate provirus through NF-kappaB (NF-ƙB) and AP-1 signal transduction. Contrast to the other potent PKC activator fellow phorbol 12-myristate 13-acetate (PMA), prostratin does not promote tumor, thus providing safe insurance to the patient. During in vitro test, prostratin

demonstrated proviral transcription induction, along with pro-inflammatory cytokine upregulation, including tumor necrosis factor alpha (TNF-α) and IL-1B. Whereas, during ex vivo experiment, prostratin and other non-tumor promoting phorbol esters 12-deoxyphorbol 13-phenylacetate (DPP) were capable of reversing latency in cell and most importantly inducing T cell activation to clear reactivated infected cells[2,5].

Although there has been no in vivo test, the obtained data thus far had shown great promise in prostratin utilization compared to current LRA combinations that can only produce secluded wanted results. Still, in order to achieve optimal results, LRA combination and adjuvant pharmacotherapy are required, especially with the heterogeneity found at different HIV-infected cell, each with distinct drug sensitivity response[2,4,6]. So far, the tested combination with synergistic reactivation result is Vorinostat, TSA, JQ1 (BRD main inhibitor, combination proved not immunosuppressive), HDACi (Romidepsin or Panobinostat), hexamethylene bisacetamide (HMBA, P-TEFb release enhancer), Galectin-9, and TLR-8 agonist (low activity in patient T cells for the record)[2].

Further study can be easily reproduced synthetically as prostratin can be easily obtained from phorbol alteration at third carbon ring through the addition of acetate side chain. Even, prostratin analogue such as phorbol-13-monoesters produces more potent result at least 10 times. Further alteration can be investigated in order to reach maximum potential[5,7,8].

3. KESIMPULAN

Proposing chronic issue to HIV-infected population, various alternatives have been explored to put an end to this never-ending ailment. The most recent inspection is focused on LRA application through shock and kill approach. However, not all candidates provide satisfactory result due to heterogenous and complex mechanism comprising HIV reactivation and eradication.

Among all candidates, prostratin stands out as a promising choice. Not only can prostratin reactivate latent HIV, but also deescalate early HIV replication cycle, increase pro-inflammatory cytokine, induce T cell and natural killer cell activation. Therefore, prostratin utilization supports immune system function needed to clear the reactivated cells in addition of reversing the latency, providing one step closer in HIV total eradication.

However, to ensure the efficacy and safety of prostratin in human, further studies are required, especially concerning any short- or long-term effects developed after prostratin usage. More investigations regarding the best model of prostratin alterations and pharmacotherapy combinations are also crucial to increase the efficacy and safety of prostratin application in human as well, ensuring remarkable result to annihilate HIV infection wholly.

DAFTAR PUSTAKA

1. Margolis DM, Garcia JV, Hazuda DJ, Haynes BF. *Latency reversal and viral clearance to cure HIV-1. Science*. 2016; 353(6297): aaf6517.
2. Spivak AM, Planelles V. *Novel latency reversal agents for HIV-1 cure*. Annu Rev Med. 2018; 69: 421-36.
3. Desimio MG, Giuliani E, Ferraro AS, Adorno G, Doria M. *In vitro exposure to prostratin but not bryostatin-1 improves natural killer cell functions including killing of CD4+T cells harboring reactivated Human Immunodeficiency Virus*. Front Immunol. 2018; 9: 1514.
4. Ait-Ammar A, Kula A, Darcis G, Verdikt R, De Wit S, Gautier V. *Current status of latency reversing agents facing the heterogeneity of HIV-1 cellular and tissue reservoirs*. Front Microbiol. 2020; 10: 3060.
5. Cragg GM, Newman DJ, Kingston DGI. *Comprehensive natural products II. Vol. 2, Natural products structural diversity-II secondary metabolites: Sources, structures, and chemical biology*. Amsterdam: Elsevier; 2010. Chapter 2, Terrestrial plants as a source of novel pharmaceutical agents; p.5-39.
6. Grau-Exposito J, Luque-Ballesteros L, Navarro J, Curran A, Burgos J, Ribera E, et al. *Latency reversal agents affect differently the latent reservoir present in distinct CD4+ T subpopulations*. PLoS Pathog. 2019; 15(8): e1007991.
7. Beans EJ, Fournogerakis D, Gauntlett C, Heumann LV, Kramer R, Marsden MD, et al. *Highly potent, synthetically accessible prostratin analogs induce latent HIV expression in vitro and ex vivo*. Proc Natl Acad Sci USA. 2013; 110(29): 11698-703.
8. Wender PA, Kee J, Warrington JM. *Practical synthesis of prostratin, DPP, and their analogs, adjuvant leads against latent HIV*. Science. 2008; 320(5876): 649-52.