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A REVIEW ON ACTION OF PHYTOCHEMICALS ON PROTEASE ENZYME AS ANTIVIRAL AGENTS

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ABSTRACT

Recent worldwide outbreaks of viral infections have increased the thirst to discover and introduce antiviral agents to combat it. The bioactive compounds obtained from plant sources, especially flavonoids have protease inhibition activities so these may be most effective for control of viral infections. A natural product used in prevention of viral infection is beneficial, because of fewer side effects and low toxicity profile compared to compounds of synthetic origin. In the present review, we summarize natural products with preventive activities against viral infection. In addition, we also covered conventional therapy used for treating viral diseases with their mechanism of action. The present review may provide information on the use of these compounds for the prevention of viral diseases

Keywords*:* - Antiviral agents; Protease enzyme; phytochemicals; targets

INTRODUCTION:

The World Health Organization (WHO) suggested that about 72 million people had already been infected with the human Immuno-deficiency Virus (HIV) global in 2017 (WHO, 2018). of these re-cords, the sub-Saharan Africa changed into the most closely affected location, accounting for over 69% of all infected cases. The Joint United countries (UNAIDS record) (2018) states that although there may be a steady decline in obtained Immune Deficiency Syndrome (AIDS) associated illnesses over the past decade; however, the global fee of latest HIV infections is not falling fast sufficient to attain the milestones set in vicinity by means of 2020 (WHO, 2018).Of the enzymes concerned inside the replication cycle of HIV in human immune cells, the HIV protease enzyme is one of the maximum vast enzymes required to provide mature and infectious HIV virions. This has allowed the enzyme to be the maximum protuberant awareness for anti-HIV inhibitors (scholar, 2011). The protease enzyme is a C2-symmetric active homodimer, consisting of a non-covalently linked dimer of 99 amino acid residues each to shape an energetic homodimer. the two monomeric chains bring together to shape an enclosed tunnel blanketed by way of flaps that ordinarily “open and close” upon substrate binding (Levy and Caflisch, 2003). The powerful activity of HIV protease within the viral cycle is critical for the maturation of infectious HIV virions (Brik and Wong,2003). consequently, there may be no question that inhibition or inactivation of the enzyme will result to the production of much less feasible and non-infectious virions and will eventually cause a discount inside the spread of the injection to vulnerable hosts or cells.

Viral replication by means of HIV is inhibited by way of protease inhibitor pills (PIs) by means of binding to the HIV proteases and finally obstructing the proteolytic cleavage of the protein precursors which are crucial for making of mature HIV virions.[1-3]

Protease inhibitors with Antiviral Activity:

Saquinavir:

The Brand name: Invirase, evolved through F. Hoffmann-los angeles Roche Ltd (Basel, Switzerland), changed into the first FDA-authorized HIV protease inhibitor used inside the treatment of patients with AIDS (in 1995). The original design for the precursor of saquinavir comprised a proline at the P1′ website and a phenylalanine at the P1 web site. The intent is that HIV-1 protease cleaves the substrate between a phenylalanine and a proline, even as mammalian proteases do no longer cleave substrates containing proline on the P1′ web page. within the final shape of saquinavir, the proline turned into changed by a z (S, S, S)-decahydro-isoquinoline- 3-carbonyl (DIQ) group to enhance the inhibitory efficiency. The

carbonyl of the DIQ group contacts the bridging water molecule, which interacts with the inhibitor and the flaps of HIV-1 protease.10 The imply 50% effective awareness (EC50) of saquinavir against HIV-1 in MT4 cells is 37.7 nM.11 The adult dose is twice every day saquinavir 1,000 mg in mixture with ritonavir 1 00 mg. Few side outcomes associated with saquinavir had been reported.[4][5].

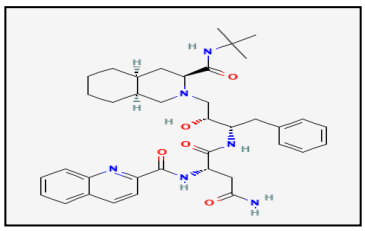

Fig No. 1: Saquinavir

Indinavir:

The Brand name: Crixivanbecame advanced by using Merck & Co, Inc., (Whitehouse Station, NJ, America) and approved in 1996.an advantage of indinavir is its powerful inhibition of each HIV-1 and HIV-2, at the same time as the drawback is the quick lower in the concentration of circulating indinavir. The low plasma concentration of indinavir normally results in remedy failures further, the low solubility of indinavir may result in the development of kidney stones. moreover, indinavir should act as an aggressive inhibitor of the cytoplasmic glucose binding website of GLUT4,15 and lipodystrophy syndrome are strongly related to indinavir similarly, indinavir has a quick performing time and calls for a dosage of 800 mg every 8 hours. For those motives, indinavir has been replaced by way of 2nd-generation protease inhibitors.[6],

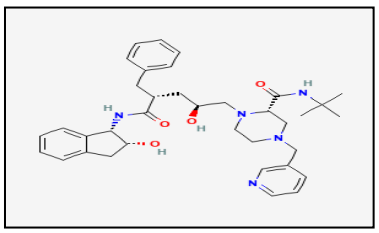

Fig No.2: Indinavir

Ritonavir:

The Brand name: Norvir, evolved by means of Abbott Laboratories (Abbott Park, IL, united states of America) and authorized with the aid of the FDA in 1996, turned into initially designed as an HIV protease inhibitor but it was located later that ritonavir boosts the circulating awareness of other HIV protease inhibitors by means of inhibiting cytochrome. regarding the molecule shape, the isopropyl thiazolyl P3 organization in ritonavir is longer

than that in other FDA-approved HIV protease inhibitors. As a remarkably mighty inhibitor of P450 3A4, a subtherapeutic dose of ritonavir has been used to reinforce the plasma awareness of 2nd generation of HIV protease inhibitors, because HIV protease inhibitors are significantly metabolized by using cytochrome P450 3A4.18 Ritonavir inhibits cytochrome P450 3A4 isoenzyme and stops the metabolism of other protease inhibitors. Normally, boosted HIV protease inhibitors enhance the side-effect and toxicity profile of HAART regimens. but, cytochrome P450 3A4 polymorphism, which encodes a non-practical protein, affects the metabolism of boosted HIV protease inhibitors, causing a better plasma attention of HIV protease inhibitors and elevated toxicity.19 Ritonavir-boosted protease inhibitor regimens require less common dosing, which benefits sufferers. However, better doses should lead to hyper lipidaemia in AIDS patients or wholesome volunteers taking ritonavir.[7],[8]

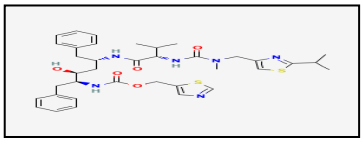

Fig No.3: Ritonavir

Nelfinavir:

The brand name: Viracept turned into advanced by Agouron pharmaceuticals (Pfizer, Inc., New York, New York, U.S.A.) and permitted in 1997. One terminus of the nelfinavir molecule has the identical DIQ organization as saquinavir. the other terminus of nelfinavir consists of a 2-methyl-3-hydroxybenzamide group. The S-phenyl group on the P1 website was designed to magnify the efficiency of this inhibitor. The EC50 of nelfinavir is 30–60 nm. The favoured routine of nelfinavir is 1,250 mg orally, two times a day. The most common side effects associated with nelfinavir are diarrhoea and nausea.[9].

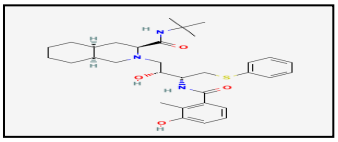

Fig No.4: Nelfinavir

Lopinavir:

The Brand name: Kaletra containing lopinavir and ritonavir, from Abbott Laboratories, changed into authorized by the FDA in 2000 and became evolved as a ritonavir-based totally agent. The centre region of lopinavir, a hydroxy ethylene dipeptide isostere, is the same as that of ritonavir. The P2 and P2′ group are altered in lopinavir relative to ritonavir. The 5-thiazolyl P2 group of ritonavir is replaced by using a phenoxy acetyl group, and the two -

isopropyl thiazolyl P2′ group of ritonavir is changed by a six-member cyclic urea. In well-known, the brand new P2 and P2′ agencies are smaller on the way to lower the contact with incredibly variable residues at the eight 2 web pages of HIV-1 protease.22 The substitution of the P2 and P2′ businesses improve the inhibitory efficiency of lopinavir in opposition to the drug-resistant versions of HIV-1 protease.[10],[11].

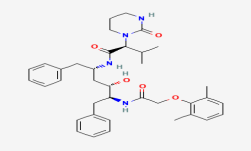

Fig No. 5: Lopinavir

Amprenavir:

The Brand name: Agenerase, evolved by Vertex pharmaceuticals included, (Boston, MA, America) and permitted in 1999, has a benzyl group at the P1 site and an isobutyl institution at the P1′ site. The P1′ organization and the phenyl amide P2′ group are linked by using a sulphonamide. The asymmetry of the P1 and P1′ groups might also choose the inner pseudosymmetry of HIV-1 protease. Amprenavir incorporates fewer chiral centres than do preceding HIV protease inhibitors. This development simplifies the chemical synthesis and increases the oral availability. The dosage of amprenavir is 1,200 mg orally, two times a day. Amprenavir is much less effective on HIV-2 protease than on HIV-1 protease.27 The EC50 of amprenavir has ranged from 12–eighty nm. Amprenavir and its prodrug, fosamprenavir, purpose the facet impact of benign skin rash.[12]

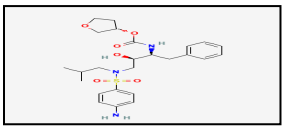

Fig No. 6: Amprenavir

Protease Enzyme:

In the HIV life cycle, protease is an important detail for viral maturation. The HIV protease is a homodimeric aspartyl protease, and each monomer consists of ninety-nine amino acid residues with a catalytic Asp at role 25 (discern 1). HIV-1 protease cleaves Gag and Gag-Pol polyprotein precursor encoded by the HIV-1 virus genome at 9 processing sites to produce mature active proteins. The Pol polyproteins is first cleaved off from the Gag-Pol polyproteins after which similarly digested into protease, reverse transcriptase (p51), RANase H (p15), and integrase. The lively web site isn't fully exposed, being included by way of two flexible β-hairpin flaps. The flaps want to open to allow the substrates to get right of entry to

the energetic site. The HIV-1 protease enzyme interest can be inhibited by means of blocking the active site of the protease.[13],[14].

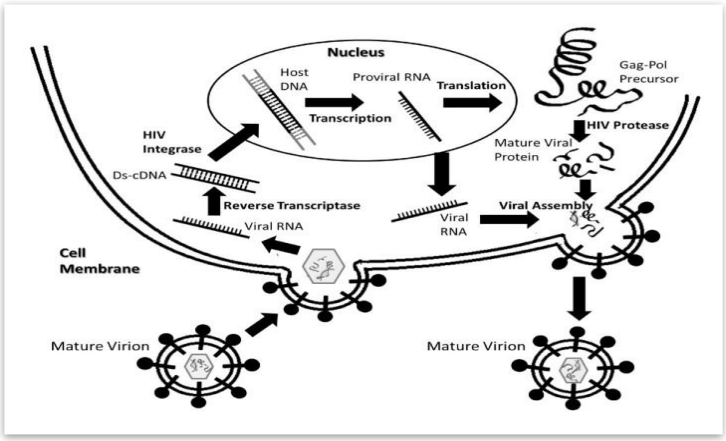

Fig No. 7: Mechanism of Protease Enzyme

Phytochemicals acts on Protease Enzyme:

Fisetin & Rutin:

Enterovirus A71 (EV-A71) reasons extreme complications: encephalitis, pulmonary edema, and death. No effective drug has been permitted for clinical use. This study investigated the antiviral results of flavonoids against EV-A71. An in vitro inhibitor screening assay using recombinant EV-A71 3C protease (3Cpro) validated fisetin and rutin inhibiting 3Cpro enzymatic activity in a dose-established way. Cell-based fluorescence resonance energy transfer (be troubled) assay with an EV-A71 3Cpro cleavage motif probe also confirmed that fisetin and rutin inhibited the replication of EV-A71 in cells. a virus replication assay indicated that fisetin and rutin decreased significantly the EV.A71-triggered cytopathic effect and viral plaque titers in RD cells culture. The IC (50) values of plaque reduction against EV-A71 were 85 uM for fisetin and 110 uM for rutin. Healing indices (CC50/IC50 of plaque discount assays) of fisetin and rutin handed. The study indicates that fisetin and rutin inhibit the replication of EV-A71.[15],[16],[17]

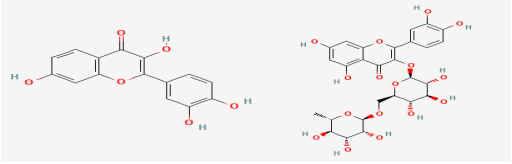

Fig No. 8: Fisetin **Fig No. 9: Rutin**

Gallic Acid:

HIV-1 Protease (HIV-1 PR) enzymes are vital for accurate assembly and maturation of infectious HIV retroviruses. The significant function of HIV-1 protease in viral replication

has made it an ability drug target. Inside the current beyond, phytochemical Gallic Acid (GA) derivatives were screened for protease inhibitor interest. In this present examine, one of the GA analogues (GA4) emerged as an effective drug candidate for HIV-1 PR inhibition, and docking results showed it to be similar with anti-HIV drugs, darunavir and amprenavir. The GA4 by-product furnished a lead for designing more effective HIV-1 PR inhibitors.[18-20].

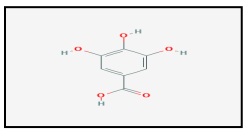

Fig No. 10: GallicAcid

Pthalic Acid:

Salts of the anti-HIV drug lamivudine, with phthalic acid and salicylic acid as counterions, have been investigated in this have a look at. Neither the packing of the (lamivudine)+(phthalic acid)− ion pairs nor the conformation of the lamivudine moiety itself have been just like the ones located in different multicomponent molecular salts of the drug, such as hydrogen maleate and saccharinate ones, despite the fact that all three salts crystallize within the identical P212121 orthorhombic space group with similar unit cell metrics. Lamivudine salicylate assumes a distinctive crystal shape to the ones of the hydrogen maleate and saccharinate salts, crystallizing within the P21 monoclinic area group as a monohydrate whose (lamivudine)+(salicylic acid)− ion pair is assembled via hydrogen bonds with cytosine as a two donor to both oxygens of the carboxylate, including inside the pairing of lamivudine with a phthalic acid counterion. In lamivudine salicylate monohydrate, the drug conformation is related to the hydrogen maleate and saccharinate salts. However, any such conformational similarity is not related to the intermolecular interaction styles. Lamivudine and water molecules alternate into helical chains in the salicylate salt monohydrate.[21],[22].

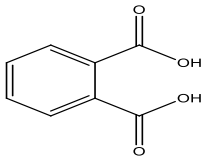

Fig No. 11:Pthalic Acid

Luteolin:

Luteolin inhibited HIV-1 independently of viral access and reverse transcription steps. A. effect of luteolin on viral entry. TZM-bl cells (6610 five) in six well tissue culture plates were pretreated with luteolin (5 and 10 mM) or vehicle for 1 h, then inflamed with HIV-1 infection (p24 = 250 ng/ml) for 2 h at 37uC. After infection, cells were briefly treated with 0.2%

trypsin-EDTA and washed appreciably to cast off mobile-membrane bound virus debris. Six h put up-infection, cells were trypsinized and lysed. p24 stages were anticipated in cell lysates after normalization of protein concentrations (BCA approach) and in HIV-1 inflamed culture supernatant (HIV-sup). The results are offered as the amount of p24 gift per mg of proteins in cell lysates. B. TZM-bl cells (6610 five) in six-well tissue culture plates have been pretreated with luteolin (10 mM) or DMSO for 30 min, then infected with HIV-1 NLENG1 (p24, 250 ng/ml) for 2 h. At 6 h after contamination, cells had been dealt with in brief with 0.2% trypsin and washed. Genomic DNA turned into harvested from HIV-infected cells. 200 ng of overall DNA changed into used as a template for quantification of viral DNA via actual-time PCR the use of Tat primers and normalized to GAPDH signals. In parallel, 500 ng HIV-1 proviral DNA (pHIV) was transfected as a effective control.[23-24].

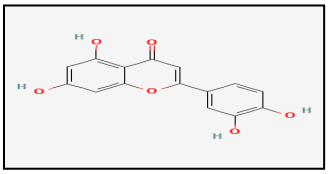

Fig No. 12: Luteolin

CONCLUSION

In this review involved recent discoveries of antiviral phytochemicals active against Protease enzyme. Overall, herbal medicine has been used to treat Viral diseases. As scientific technologies have been developed and the pathological pathways of viral infections discovered, specific study can be done to interpret the usage of plant products as phytochemicals, identify the active constitutions for the Viral diseases, and explore the possible mechanisms of action. These studies will significantly help research areas to discover novel antiviral drugs from novel natural product leads by using medicinal chemistry approaches and to explore their mechanistic pathways through study of pharmacological activity.

REFERENCES

1. Idowu Kehinde, Pritika Ramharack, Manimbulu Nlooto, Michelle Gordon. ELSEVIER The pharmacokinetic properties of HIV-1 protease inhibitors: A computational perspective on herbal phytochemicals. 2019. page no:1
2. UNAIDS. Global Report: UNAIDS Report on the Global AIDS Epidemic 2010. Geneva: UNAIDS; 2010.
3. Riddler SA, Haubrich R, DiRienzo AG, et al; AIDS Clinical Trials Group Study A5142 Team. Class-sparing regimens for initial treatment of HIV-1 infection. N Engl J Med. 2008;358(20):2095–2106.
4. Hruz PW. HIV protease inhibitors and insulin resistance: lessons from in-vitro, rodent and healthy human volunteer models. Curr Opin HIV AIDS. 2008;3(6):660–665.

5. Soontornniyomkij V, Umlauf A, Chung SA, et al. HIV protease inhibitor exposure predicts cerebral small vessel disease. AIDS. 2014;28(9):1297–1306.
6. Cameron DW, da Silva BA, Arribas JR, et al. A 96-week comparison of lopinavir-ritonavir combination therapy followed by lopinavir-ritonavir monotherapy versus efavirenz combination therapy. J Infect Dis. 2008;198(2):234–240.
7. Paton NI, Kityo C, Hoppe A, et al; EARNEST Trial Team. Assessment of second-line antiretroviral regimens for HIV therapy in Africa. N Engl J Med. 2014;371(3):234–247.
8. J.W., Matthews, D.A., Patick, A.K., 2005. Conservation of amino acids in human rhinovirus 3C protease correlates with broad-spectrum antiviral activity of rupintrivir, a novel human rhinovirus 3C protease inhibitor. Antimicrob. Agents Chemother. 49, 619–626.
9. Singh, Anjali; Pal, Tapan Kumar (2015). Docking analysis of gallic acid derivatives as HIV-1 protease inhibitors. International Journal of Bioinformatics Research and Applications, 11(6), 540–. doi:10.1504/IJBRA.2015.073239
10. I .Kehind,P .Ramharack,M .Nlooto,M .Gordon-Heliyon.2019-ELSEVIER.
11. S Tewtrakul, H Miyashiro, N Nakamura… - Phytotherapy …, 2003 - Wiley Online Library.
12. Krohn A, Redshaw S, Ritchie JC, Graves BJ, Hatada MH. Novel binding mode of highly potent HIV-proteinase inhibitors incorporating the (R)-hydroxy ethylamine isostere. J Med Chem. 1991;34(11):3340–3342.
13. US Food and Drug Administration. Roche, Fortovase® (saquinavir). Silver Spring, MD: US Food and Drug Administration; 2003. Availablefrom:http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/20828s015ppi. pdf Accessed March 25, 2015.
14. González de Requena D, Gallego O, de Mendoza C, Corral A,Jiménez-Nácher I, Soriano V. Indinavir plasma concentrations and resistance mutations in patients experiencing early virological failure.AIDS Res Hum Retroviruses. 2003;19(6):457–459.
15. Hresko RC, Hruz PW. HIV protease inhibitors act as competitive inhibitors of the cytoplasmic glucose binding site of GLUTs with differingaffinities for GLUT1 and GLUT4. PLoS One. 2011;6(9):e25237.
16. Viraben R, Aquilina C. Indinavir-associated lipodystrophy. AIDS. 1998;12(6):F37–F39.
17. Kempf DJ, Marsh KC, Kumar G, et al. Pharmacokinetic enhancement of inhibitors of the human immunodeficiency virus protease by coadministration with ritonavir. Antimicrob Agents Chemother. 1997;41(3):654–660.
18. Zeldin RK, Petruschke RA. Pharmacological and therapeutic properties of ritonavir-boosted protease inhibitor therapy in HIV-infected patients. J Antimicrob Chemother. 2004;53(1):4–9.
19. López Aspiroz E, Cabrera Figueroa SE, Iglesias Gómez A, Valverde Merino MP, Domínguez-Gil Hurlé A. CYP3A4 polymorphism and lopinavir toxicity in an HIV-infected pregnant woman. Clin Drug Investig.2015;35(1):61–66.
20. Purnell JQ, Zambon A, Knopp RH, et al. Effect of ritonavir on lipids and post-heparin lipase activities in normal subjects. AIDS. 2000;14(1):51–57.
21. Max B, Sherer R. Management of the adverse effects of antiretroviral therapy and medication adherence. Clin Infect Dis. 2000;30 Suppl 2: S96–S116.
22. Sham HL, Kempf DJ, Molla A, et al. ABT-378, a highly potent inhibitor of the human immunodeficiency virus protease. Antimicrob Agents Chemother. 1998;42(12):3218–3224.
23. Noor MA, Parker RA, O'Mara E, et al. The effects of HIV protease inhibitors atazanavir and lopinavir/ritonavir on insulin sensitivity in HIV-seronegative healthy adults. AIDS. 2004;18(16):2137–2144.
24. Manfredi R, Sabbatani S. Serious, multi-organ hypersensitivity to lopinavir alone, involving cutaneous-mucous rash, and myeloid, liver, and kidney function. AIDS. 2006;20(18):2399–2400.