Review

Medicinal properties of *Ficus sp.* as anti-HIV

Dwi Wahyu Indriati[1]*, Dwi Wahyu Indrian[2]

1 Department of Health Science, Faculty of Vocational Studies, Universitas Airlangga, Indonesia
2 National Research and Innovation Agency, Indonesia

*Corresponding Author:
Department of Health Science,
Faculty of Vocational Studies,
Universitas Airlangga,
Surabaya 60286, East Java, Indonesia
E-mail address: dwiwahyu.indriati@vokasi.unair.ac.id

ABSTRACT:

This paper reviewed the potential of *Ficus* sp as anti-HIV. Due to the increasing incidence of drug resistance mutation among HIV patient with antiretroviral therapy, the need for new therapy is increasing. Thus, the option fell upon herbal medicine. One of those potentially acknowledged herbal medicine is *Ficus* sp which already known to have antibacterial and antioxidant properties. In this paper, we ruled out the potential mechanism of action of phytochemicals found in *Ficus* sp in inhibiting viral entry, and block HIV enzymes such as reverse transcriptase, integrase and protease.

KEYWORDS: *Ficus sp., Moraceae,* antiviral, antioxidant, antibacterial, therapeutic

INTRODUCTION:

Human Immunodeficiency Virus (HIV) is still considered as an infectious disease that gains much attention around the world for leading acquired immunodeficiency syndrome. This virus specifically attacks the CD4 cells (T cells) of the immune system that fight infection. HIV infects cell target in several steps including membrane attachment, receptor binding, fusion, uncoating, reverse transcription, integration, and maturation. HIV cannot be completely eradicated from an individual`s body once infected[1,2], however, its replication rate can be suppressed with antiretroviral therapy. HIV infects cell target in several steps including membrane attachment, receptor binding, fusion, uncoating, reverse transcription, integration, and maturation.

The first antiretroviral (ARV) approved for HIV therapy was zidovudine, known as the nucleoside analog reverse transcription (NRTI). This invention was successfully followed by other reverse transcriptase (RT) inhibitors therapy[3]. Currently, there are five classes of ARVs have become available. Those are licensed for inhibiting RT, NRTI and non-nucleoside analog reverse transcription (NNRTI), protease (PI), fusion (F1), receptor binding (CCR5), and integrase (INI)4. The inhibition from one of these therapies will prevent HIV to infect CD4 cells, thus reducing HIV concentration in the blood. The combination of ARV therapy therefore will help in the fastest-acting drug[4]. Recently the emergence of drug resistance mutations raising concern over the effectiveness of ARV in treating the patient with HIV[5,6]. Several studies have been shown that drug resistance mutation slowly appears in every part of Indonesia such as in Jakarta, Bali, Riau, Maumere[7–10]. Drug resistance mutations can appear from lifetime ARV consumption or transmitted from patients with ARV to healthy individuals known as transmitted drug resistance (TDR)[11]. Thus, currently, researchers are racing to invent newly developed anti-HIV.

One alternative drug development is using herbal medicine because it provides effective and more affordable results. The studies on natural products against HIV have started since the 1990s, although most of these studies are still in vitro. But traditional Chinese medicine (TCM) interventions in 12 clinical trials involving 881 patients with AIDS showed that plasma viral load in patients on TCM therapy were reduced compared to placebo, suggesting significant potential of natural products to inhibit HIV[12]. In this review we will focus on discussing the potential of *Ficus sp.* as anti-HIV. Our previous study using *Ficus fistulosa* extract[13] has been showed inhibition of HIV replication in vitro. And further studies are required to verify its active compound which act as anti-HIV and its mechanisms that inhibit HIV (viral entry inhibition or HIV enzymes inhibition).

POTENTIAL OF *FICUS SP.* AS ANTIVIRAL AGENT:

Genus *Ficus* from the family *Moraceae* is known as fig trees which has about 850 species that can be found throughout the pantropics. extending to subtropical regions, from America, Africa to Asian-Australian regions[14,15]. This genus contains six subgenera based on ribosomal DNA sequences and morphology; *Pharmacosycea, Urostigma, Ficus, Sycidium, Synoecia, Sycomorus*[16]. Ficus can be found in form of woody trees, shrubs, or climbers often with adventitious roots (liana), hemiepiphytes, epiphytes. Ficus also well known for its unique inflorewcences, namely figs or syconia and its milky latex[14,17]. *Ficus* species has been long considered as sources of food (especially for *Ficus* carica that produces fruits), medicinal plants[17–19] and some of *Ficus* species use as indoor or outdoor ornamental plant[14].

Ficus species excrete health benefit with their phytochemical content. Phytochemicals are secondary metabolites that are produced by plants which may give plants with specific color, odor or flavor for protection from predators and reproductions[20,21]. Phytochemicals compounds have been classified into six major categories based on its chemical structures. Those are polyphenols (phenolics), alkaloid, carotenoids, organosulfur compounds, terpenoids, nitrogen containing compounds. Polyphenol as the largest category of phytochemicals consist of five main classes i.e. phenolic acids, flavonoids, stillbenes, coumarins, tannins. Phytochemicals compounds, such as polyphenol (i.e. phenolic acids, flavonoids, tannins, stilbenes, coumarins), alkaloid, carotenoids, and terpenoids are known to have antiviral properties[22].

Member of *Ficus* sp. have antiviral effects against DNA-containing virus families (Herpesviridae) and RNA-containing virus families (Picornaviridae, Retroviridae, Flaviviridae) (Table 1).

Table 1. Active substances which have antiviral properties in the plants from Genus *Ficus*.

Species	Part of *Ficus*	Active substance	Antiviral mechanism
Ficus carica	Latex	Phenol-detected compound: Caffeic Acid, 3.4-Dihydroxybenzoic acid, p-OH-Phenylacetic acid, p-Coumaric acid, Luteolin, N-argenine, and Ferulic acid[23].	Inhibition multiplication of several virus including herpes simplex type 1 (HSV-1), echovirus type 11 (ECV-11) and adenovirus (ADV)[23].
Ficus benjamina	Leaf, Fruit	Flavone glycoside, quercetin 3-O-rutinoside, kaempferol 3-O-rutinoside and kaempferol 3-O-robinobioside[24].	Multiplication inhibition of Herpes Simplex Virus-1 and 2 (HSV-1 and HSV-2), also Varicella-Zooster Virus (VZV)[25].
Ficus religiosa	Bark	Methanol extract which contain saponin, flavonoids, tannins and steroids were active against RSV[26]. Saponins, carbohydrates, flavonoids and tannins (water extracts) were active for RSV[26].	Antiviral against respiratory syncytial virus (RSV) and human rhinovirus (HRV)[26]. Antiviral against Herpes Simplex Virus-2 (HSV-2)[27].
Ficus fistulosa	Leaf	Flavonoids, tannoids and chlorophyll[28].	Antiviral against Hepatitis C Virus (HCV)[29].
Ficus virens	Leaf	Flavonoids: quercetin-3-O-α-D-arabinopyranoside (2), quercetin-3-O-β-D-galactopyranoside[30]. Flavonoids: quercetin, quercetin-3-O-β-D-galactopyranoside, vogelin J[30].	Antiviral against Hepatitis A virus[30]. Antiviral against Coxsackie B4 Virus[30].
Ficus septica	Fruit, Heartwood, Leaf and Stem	Unknown	Antiviral against Dengue Virus -1 and 2 (DENV-1 and DENV-2)[31].
Ficus benghalensis	Leaf, aerial root	Quinic acid and stigmasterol[32].	Antiviral against HV-1[33].
Ficus infectoria	Leaf		Antiviral against HIV-1[33]
Ficus cycamorus	Stem bark	Unknown	Antiviral against HIV-1 [34]
Ficus polita	Whole	Unknown	Antiviral against reverse transcriptase enzyme of HIV-1 and HIV-2[35].
Ficus glomerata	Wood	Aloe-emodin; 1,3,6-trihydroxy-8-methyl-anthraquinone [36].	Antiviral against integrase enzyme of HIV-1 [36].

Since the data on *Ficus sp*. as anti-HIV is somewhat scarce, we would like first to know which kind of phytochemical responsible for inhibiting HIV.

PHYTOCHEMICAL COMPOUNDS AS ANTI-HIV

Several plants have been shown to owned phytochemicals which inhibit HIV-1. HIV-1 inhibition can occur early from viral entry, inhibit HIV-1 enzymes (reverse transcriptase, protease and integrase) and also inhibit HIV-1 maturation[37]. In this review we will focus on viral entry and HIV-1 enzyme inhibition. In this review, we would like to list several phytochemicals found in other herbal medicine and compare it with those phytochemicals found in *Ficus sp,* which act as viral entry inhibition and HIV enzymes inhibition. Several key phytochemicals shown to have affect in inhibiting HIV in several stage of its life cycle (Figure 1). Finally, in the last part of this chapter, we will discuss several phytochemicals found in *Ficus sp*, its potential as anti-HIV and several shortcomings that hinder anti-HIV research.

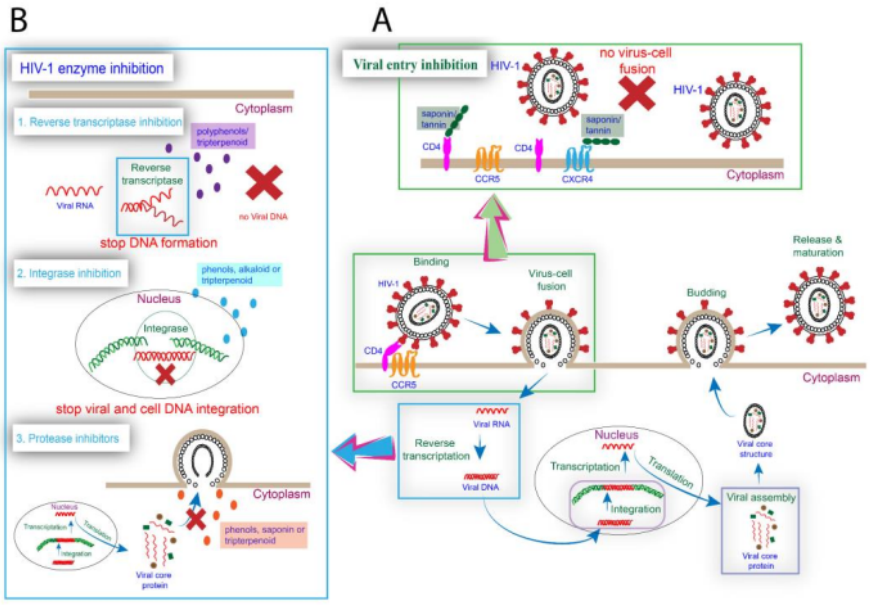

Figure 1. Proposed potential inhibition of HIV infection stage by phytochemical compounds of *Ficus* sp. (A) Viral entry inhibition. Phytochemicals of *Ficus* sp. bind to CD4 cells or the CXCR4 protein, blocking the attachment of the HIV virus to host cell. Thus, HIV virus cannot enter and infect host cell; (B) HIV enzyme inhibition. Phytochemicals of *Ficus* sp. suppress the activity of HIV enzyme (reverse transcriptase, integrase, protease) preventing DNA formation for new virus, stopping viral and host cell DNA integration, and inhibiting virion maturation, respectively.

Saponin, Tannin and Quinic acid as viral entry inhibitors

Inhibition can take place even before HIV-1 enter CD4 cells. HIV-1 entry include multiple steps with viral envelope gp120 and gp41 mediate attachment, and binding to CD4 receptors and its co-receptor binding (CXCR4 and CCR5)[38,39]. The viral entry inhibition usually targeted CD4 binding, coreceptor binding and blocking gp41 conformational changes which allow viral fusion[39].

Saponin fraction from *Psidium guajava* leaf could impede HIV-1 mediated cell fusion by obstructing HIV-1 gp41 six helical bundle formation[40]. Other type of saponin found in *Tieghemella heckelii* fruits namely arginine, and tieghemelin strongly inhibit HIV entry in a cell fusion assay[41]. Tannins especially gallotannin extracted from *P. amarus* also showed interreference with gp120, thus it impaired gp120-CD4 binding. Purified gallotannin (Geraniin and Corilagin) having high potency in inhibit gp120-CD4 binding[42]. The methanol extract of aerial parts of *Helichrysum populifolium* showed inhibition in HeLa-SXR5 cells (which expressed CXCR4 and CCR5 chemokine receptors). The active compound found in this extract were from dicaffeoylquinic acid derivatives include 3,4-dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid and 4,5-dicaffeoylquinic acid as well as two tricaffeoylquinic acid derivatives, i.e., 1,3,5-tricaffeoylquinic acid and either 5-malonyl-1,3,4-tricaffeoylquinic or 3-malonyl-1,4,5-tricaffeoylquinic acid [43].

Meanwhile in vitro analysis using *Ficus polita* extract can inhibit cell fusion in early cytopathic effect in MOLT4 cell co-cultured with MOLT4/HIV[28]. Other studies in *Ficus benghalensis* also showed it contained quinic acid which act against HIV-1 RT and Integrase enzyme also inhibit gp120 binding to CD4[32,44]. Thus, based on these studies there is possibility that *Ficus sp* can act as antiviral through viral entry inhibitors.

Polyphenols, Triterpenoid as HIV-1 reverse transcriptase inhibitors

The reverse transcriptase enzyme is crucial in converting viral RNA into DNA[45]. Thus, inhibiting this enzyme could inhibit RNA-DNA conversion. The mechanism of action from several herbal plants act as RT inhibitors can be divided into two mechanism, mimics nucleoside analogues and pleiotropic effects. Non-nucleoside binds to HIV-1 RT and block RT action by an allosteric mechanism of action[46,47]. While in review by Chinsembu in 2019, they

listed several phytochemicals that actively act against HIV-1 RT are proteins, coumarins, alkaloid, xanthones, flavonoids, polyphenols, terpenoids, polysaccharides. But in *Ficus polita* studies, the active compound corresponds to anti-HIV is still not known. So, it needs further fractionation to rule out an active compound act against HIV.

The crude extract from *Treculia acuminata Baill, Treculia Africana* Decne. Ex Trecul, *Treculia obovoidea* N.E. Br and *Morus nigra* Thunb were used to assess its anti-HIV potential. The extract was obtained from twigs and leaves from three species of family Moraceae. The investigated extract was showed anti-reverse transcriptase activity with concentration 200μg/ml with highest value were noted from *T. obovoidea* (87.34%), *T. Africana* (86.72%) and *T.acuminata* (72.51%)[48]. The phytochemical which showed as anti RT enzyme were triterpenes, coumarins saponin, phenols and flavonoids[48], gallic acid, quercetin and linoleic, palmitic, oleic acids and kuwanon-L[49,50]. While research with in silico approach also found ten compounds were suitable for inhibiting HIV-1 reverse transcriptase inhibitor such as mulberrin, plucheoside A, vitexilactone, brucine N-oxide, cyanidin e-arabinoside, alpha-mangostin, guaijaverin, erycristalgallin, morusin and sanggenol N[51]. Punicalin and puniacortein C also inhibit HIV replication. Tannin from *T. catappa* also shown to inhibit RT though mechanism of inhibition is remain unknown[52,53].

Flavonoid, Phenols, Alkaloid and Triterpenoid as HIV-1 integrase inhibitor

Integrase enzyme has been attracted as therapeutical target for anti-HIV, since it has no homologue in human body. Integrase enzyme act as catalysator for viral DNA integration into human genome[54]. The ethanol extract from *Mimusops elengi* leaves showing inhibition against HIV-1 integrase enzyme. Further assay using anti-HIV1 assay guided purification of crude ethanol extract showed a mixture of epigallocatechin and gallocatechin from catechin class of phytochemical (flavonoid) as potential anti integrase[55]. Other gallocatechin isolated from Nelumbo nucifera Gaertn also showed anti-HIV-1 integrase[56]. Four catechin known to interfere the interaction with DNA virus thus it reduces the integrase activity. Those four catechin are catechin gallate, epigallocatechin gallate, gallocatechin gallate and epicatechin gallate[56,57].

From phenolic compound known as ferulic acid and alkaloid kind of phytochemicals, tryptamine showed anti-HIV-1 integrase enzyme[58]. Lupeol, active compound of *Betula alnoides* as one kind of triterpenoid also showed potent inhibition against HIV integrase[59]. Lupeol will interact with Asp64, His67 and Lys159. Asp64 is responsible for 3`processing While His67 and Lys159 participate in strand-transfer reaction of integration process[59]. *Ficus glomerata* also showed anti-HIV- 1 integrase since it contained aloe emodin and 1,3,6-trihydroxy-8-methyl-anthraquinone from phenolic compound[29].

Saponin, Triterpenoid and Phenols as HIV-1 protease inhibitors

Protease enzyme is required for maturation and infectivity of HIV[61]. The chloroform extract from *Bosenbergia pandurate* rhizome showed inhibition against HIV-1 protease enzyme. While methanol extract of *Bosenbergia pandurate* rhizome, *Alpinia galanga* rhizome also showed potent protease inhibition at 100ug/ml concentration [62]. The responsible anti-HIV protease found in *Acacia pennata* were new saponin which separated and purified with column chromatography method. This new saponin compound is known as 21β-*O*-[(2*E*)-6-hydroxyl-2,6-dimethyl-2,7-octadienoyl]-bitheduloside G showed anti-HIV-1 PR activity[61].Several triterpenoids also showed a potential for PR inhibition such as oleanolic acid, ursolic acid, uvaol, maslinic acid and 2α and 19α-dihydroxy-3-oxo-12-ursen-28oic acid[63–65]. Triacyglycerol, linoleic acid and ergosterol could block HIV-1 PR[66]. From phenols phytochemicals, epigallocatechin gallate exhibit anti-HIV-1 PR[67]. However, further studies are still needed to check the possibility whether the phenols, saponin or triterpenoid contained in *Ficus sp* can be used as anti-HIV through HIV-1 protease inhibitors route.

LIMITATION IN ANTI-VIRAL RESEARCH

The promising potential of anti-viral properties in plants as general not only from *Ficus sp*. unfortunately has been restricted by the imperfection in the existing screening tests before being developed as antiviral drug. Traditional in vitro techniques of analyzing anti-viral includes plaque inhibition assay, plaque reduction assay, inhibition of virus-induced cytopathic effect, end point titer determination assay, virus yield reduction assay, reduction or inhibition of the synthesis of virus-specific polypeptides, immunological assays detecting viral antigens, and viral enzyme inhibition-based assays[68,69]. The aforementioned methods have been used successfully for screening large number of diverse anti-viral agents. However, these methods also have some drawbacks related to safety, long assay period,

impractical, experimental-biased read-out and high cost. More importantly, the available methods are unable to differentiate between mere toxic effects of agents on host cells or its selective antiviral effects. In the recent years, indeed cell-based assays have been favorable methods to evaluate antiviral properties, as it is able to monitor specific viral proteins and intracellularly screen for potent viral inhibitor with desired pharmacological properties. Nevertheless, this assay still can't be used to differentiate antiviral activity from the complexity of chemical processes in the cell[67,68]. Therefore, high throughput assays with more specificity are needed to screen medicinal plants with potential antiviral activities[70,71].

Another shortcoming in antiviral development is because it's strictly dependent on cellular metabolic process, virus only have limited number of enzyme systems that can potentially serve as inhibition target. Antiviral also expected to irreversibly block viral synthesis so that it will block cell suicide due to viral infection. Thus, normal cell synthesis can be restored[72]. It is favorable needed that antiviral has pharmacodynamic properties and not immunosuppressive. Then finally the best scenario will be that antiviral will check the infection while immune system will destroy the last virus particles[73].

CONCLUSIONS

In this review paper, we listed the phytochemical compounds that are effective as anti-HIV by disrupting HIV life cycle through viral entry and HIV enzymes inhibition. Those phytochemical compounds also can be found in some of *Ficus sp*. which is discussed here. However, only few of them have shown as an antiviral against HIV. Other species from *Ficus sp*. which contain anti-HIV phytochemical, needs further studies to prove their potential as anti-HIV agent. High throughput assays with more specificity, such as a vector-based assay technique is needed to tackle the disadvantages come along with traditional antiviral compounds testing. Another drawback hindering the study of antiviral is the focus of this research should also include the possibility that the compounds have pharmacodynamic properties which allows permanent blocking of viral synthesis while immune system will destroy the last virus particles.

CONFLICT OF INTEREST:

The authors declare no conflict of interest.

ACKNOWLEDGEMENT:

The author wanted to thank all colleague in Institute of Tropical Disease Universitas Airlangga for their suggestion in writing this article.

REFERENCES

1. Chun TW. Stuyver L. Mizell SB. Ehler LA. Mican JAM. Baseler M. et al. Presence of an inducible HIV-1 latent reservoir during highly active antiretroviral therapy. Proceeding of the National Academy of Sciences of the United Stated of America 1997; 94(24): 13193–13197. doi: 10.1073/pnas.94.24.13193
2. Marsden MD. Zack JA. Eradication of HIV: Current challenges and new directions. Journal of Antimicrobial Chemotherapy 2009; 63(1):7–10. doi: 10.1093/jac/dkn455
3. Bogner E. Holzenburg A. New concepts of antiviral therapy. Springer, Netherlands. 2006.
4. Murray JM. Kelleher AD. Cooper DA. Timing of the Components of the HIV Life Cycle in Productively Infected CD4+ T Cells in a Population of HIV-Infected Individuals. Journal of Virology 2011; 85(20):10798–10805. doi: 10.1128/jvi.05095-11
5. Hong SY. Nachega JB. Kelley K. Bertagnolio S. Marconi VC. Jordan MR. The global status of HIV drug resistance: clinical and public-health approaches for detection, treatment and prevention. Infectious Disorders Drug Targets 2011; 11(2): 124–133. doi: 10.2174/187152611795589744
6. Hosseinipour MC. Gupta RK. Van Zyl G. Eron JJ. Nachega JB. Emergence of HIV drug resistance during first- and second-line antiretroviral therapy in resource-limited settings. Journal of Infectious Disease 2013; 207(Suppl 2): 49–56. doi: 10.1093/infdis/jit107
7. Witaningrum AM. Khairunisa SQ. Ueda S. Yunifiar MQ. Indriati DW. Kotaki T. et al. Viral subtyping of HIV-1 derived from infected, drug-naive individuals in Jakarta, Indonesia. In: IOP Conference Series: Materials Science and Engineering 2018; 434(1). doi: 10.1088/1757-899X/434/1/012321
8. Indriati DW. Kotaki T. Khairunisa SQ. Witaningrum AM. Matondang MQY. Ueda S. et al. Appearance of drug resistance mutations among the dominant HIV-1 subtype, CRF01_AE in Maumere, Indonesia. Current HIV Research 2018; 16(2): 158-166. doi: 10.1088/1757-899X/434/1/012321
9. Khairunisa SQ. Masyeni S. Witaningrum AM. Yunifiar MMQ, Indriati DW, Kotaki T, et al. Genotypic characterization of human immunodeficiency virus type 1 isolated in Bali, Indonesia in 2016. HIV and AIDS Review 2018; 17(2). doi: 10.5114/hivar.2018.76375
10. Khairunisa SQ. Ueda S. Witaningrum AM. Yunifiar MMQ. Indriati DW. Kotaki T. et al. Genotypic characterization of human immunodeficiency virus type 1 prevalent in kepulauan riau, Indonesia. AIDS Resesearch and Human Retroviruses 2018; 34(6): 555-560. doi: 10.1089/AID.2018.0040

11. Takuva S. Louwagie G. Zuma K. Okello V. Durability of first line antiretroviral therapy: Reasons and predictive factors for modifications in a Swaziland Cohort. Journal of Antivirals and Antiretrovir 2012; 4(1): 14–20. doi: 10.4172/jaa.1000040
12. Salehi B. Anil KNV. Şener B. Sharifi-Rad M. Kılıç M. Mahady GB. et al. Medicinal plants used in the treatment of human immunodeficiency virus. International Journal of Molecule Sciences 2018; 19(5): 1459. doi: 10.3390/ijms19051459
13. Indriati DW. Tumewu L. Widyawaruyanti A. Khairunisa S. The activities of methanol extract, hexane and ethyl acetate fractions from Ficus fistulosa in HIV inhibition in vitro. Research Journal of Pharmacy and Technology 2020; 13(1): 187-190. doi: 10.5958/0974-360X.2020.00038.4
14. Berg CC. Corner EJH. Moraceae: Ficeae. Flora Malesiana - Series 1, Spermatophyta. 2005.
15. Awad NE. Seida AA. Hamed MA. Elbatanony MM. Hypolipidaemic and antioxidant activities of Ficus microcarpa (L.) in hypercholesterolemic rats. Natural Product Research 2011;25(12): 1202-1207. doi: 10.1080/14786419.2010.538015
16. Weiblen GD. Phylogenetic relationships of functionally dioecious Ficus (Moraceae) based on ribosomal DNA sequences and morphology. American Journal of Botany 2000; 87(9): 1342–1357. doi: 10.2307/2656726
17. Shi Y. Mon AM. Fu Y. Zhang Y. Wang C. Yang X. et al. The genus Ficus (Moraceae) used in diet: Its plant diversity, distribution, traditional uses and ethnopharmacological importance. Journal of Ethnopharmacology 2018; 226: 185–196. doi: 10.1016/j.jep.2018.07.027
18. Joseph B. Raj SJ. Phytopharmacological and Phytochemical Properties of Three Ficus Species: An Overview. International Journal of Pharma and Bio Sciences 2010; 1(4): 246-253.
19. Nawaz H. Waheed R. Nawaz M. Phytochemical Composition, Antioxidant Potential and Medicinal Significance of Ficus. In: Kahramanoglu I. Kafkas NE. Kuden A. Modern Fruit Industry. IntechOpen; 2020. doi: 10.5772/intechopen.86562
20. Martinez KB. Mackert JD. McIntosh MK. Polyphenols and Intestinal Health. In Watson RR. Nutrition and Functional Foods for Healthy Aging. 2017; 191–210.
21. Huang Y. Xiao D. Burton-Freeman BM. Edirisinghe I. Chemical Changes of Bioactive Phytochemicals during Thermal Processing. Reference Module in Food Science 2016; 1–9.
22. Ghildiyal R. Prakash V. Chaudhary VK. Gupta V, Gabrani R. Phytochemicals as Antiviral Agents: Recent Updates. Plant-derived Bioactives 2020; 279-295. doi: 10.1007/978-981-15-1761-7_12
23. Lazreg AH. Gaaliche B. Fekih A. Mars M. Aouni M. Chaumon JP. et al. In vitro cytotoxic and antiviral activities of Ficus carica latex extracts. Natural Product Research 2011; 25(3): 310–319. doi: 10.1080/14786419.2010.528758
24. Yarmolinsky L. Huleihel M. Zaccai M. Ben-Shabat S. Potent antiviral flavone glycosides from Ficus benjamina leaves. Fitoterapia 2012; 83(2): 362-367. doi: 10.1016/j.fitote.2011.11.014
25. Yarmolinsky L. Zaccai M. Ben-Shabat S. Mills D. Huleihel M. Antiviral activity of ethanol extracts of Ficus binjamina and Lilium candidum in vitro. New Biotechnology 2009; 26: 307-313. doi: 10.1016/j.nbt.2009.08.005
26. Cagno V. Civra A. Kumar R. Pradhan S. Donalisio M. Sinha BN. et al. Ficus religiosa L. bark extracts inhibit human rhinovirus and respiratory syncytial virus infection in vitro. Journal of Ethnopharmacology 2015; 176: 252–257. doi: 10.1016/j.jep.2015.10.042
27. Ghosh M. Civra A. Rittà M. Cagno V. Mavuduru SG. Awasthi P. et al. Ficus religiosa L. bark extracts inhibit infection by herpes simplex virus type 2 in vitro. Archive of Virology 2016; 161(12): 3509–3514. doi: 10.1007/s00705-016-3032-3
28. Hafid AF. Permanasari AA. Tumewu L. Adianti M. Aoki C. Widyawaruyanti A. et al. Activities of Ficus fistulosa Leave Extract and Fractions against Hepatitis C Virus. Procedia Chemistry 2016; 18(12): 179–184. doi: 10.1016/j.proche.2016.01.028
29. Wahyuni TS. Tumewu L. Permanasari AA. Apriani E. Adianti M. Rahman A. et al. Antiviral activities of Indonesian medicinal plants in the East Java region against hepatitis C virus. Virology Journal. 2013; 10(1): 1-9. doi: 10.1186/1743-422X-10-259
30. Orabi MA. Orabi EA. Antiviral and antioxidant activities of flavonoids of Ficus virens: Experimental and theoretical investigations. Journal of Pharmacognosy and Phytochemistry 2016; 5(3): 120–128.
31. Huang NC. Hung WT. Tsai WL. Lai FY. Lin YS. Huang MS. et al. Ficus septica plant extracts for treating Dengue virus in vitro. PeerJ. 2017; *PeerJ* 5:e3448. doi: 10.7717/peerj.3448
32. Verma VK. Sehgal N. Prakash O. Characterization and screening of bioactive compounds in the extract prepared from aerial roots of *Ficus benghalensis*. International Journal of Pharmaceutical Sciences and Research 2015; 6(12): 5056–5069. doi: 10.13040/IJPSR.0975-8232.6(12).5056-69
33. Palshetkar A. Pathare N. Jadhav N. Pawar M. Wadhwani A. Kulkarni S. et al. In vitro anti-HIV activity of some Indian medicinal plant extracts. BMC Complement Medicine and Therapies 2020; 20(1): 69. doi: 10.1186/s12906-020-2816-x.
34. Maregesi S. Van Miert S. Pannecouque C. Feiz HMH, Hermans N. Wright CW. et al. Screening of Tanzanian medicinal plants against Plasmodium falciparum and human immunodeficiency virus. Planta Med. 2010; 76(2): 195–201. doi: 10.1055/s-0029-1186024
35. Ayisi NK. Nyadedzor C. Comparative in vitro effects of AZT and extracts of Ocimum gratissimum, Ficus polita, Clausena anisata, Alchornea cordifolia, and Elaeophorbia drupifera against HIV-1 and HIV-2 infections. Antiviral Research 2003; 58(1): 25–33. doi: 10.1016/s0166-3542(02)00166-3
36. Bunluepuech K. Sudsai T. Wattanapiromsakul C. Tewtrakul S. Inhibition on HIV-1 integrase activity and nitric oxide production of compounds from Ficus glomerata. Natural Product Communication 2011; 6(8): 1095–1098. doi: 10.1177/1934578X1100600811
37. Rege A. Screening of Natural Products for Anti-HIV Potential: An In vitro Approach. Juniper Online Journal of Immuno Virology 2015; 1(1): 1-7. doi:10.19080/JOJIV.2016.01.555556
38. Berger EA. Murphy PM. Farber JM. Chemokine receptors as HIV-1 coreceptors: roles in viral entry, tropism, and disease. Annual Review of Immunology 1999; 17: 657–700. doi: 10.1146/annurev.immunol.17.1.657.
39. Araújo LAL. Almeida SEM. HIV-1 diversity in the envelope glycoproteins: implications for viral entry inhibition. Viruses 2013; 5(2): 595–604. doi: 10.3390/v5020595
40. Mao QC. Zhou YC. Li RM. Hu YP. Liu SW. Li XJ. Inhibition of HIV-1 mediated cell-cell fusion by saponin fraction from Psidium guajava leaf. Journal of Chinese Medicinal Materials 2010; 33(11): 1751–1754.
41. Gosse B. Gnabre J. Bates RB. Dicus CW. Nakkiew P. Huang RCC. Antiviral Saponins from Tieghemella heckelii. Journal of Natural Products. 2002; 65(12): 1942–1944. doi: 10.1021/np020165g
42. Notka F. Meier G. Wagner R. Concerted inhibitory activities of Phyllanthus amarus on HIV replication in vitro and ex vivo. Antiviral Research 2004; 64(2): 93–102. doi: 10.1016/j.antiviral.2004.06.010
43. Heyman HM. Senejoux F. Seibert I. Klimkait T. Maharaj VJ. Meyer JJM. Identification of anti-HIV active dicaffeoylquinic- and tricaffeoylquinic acids in Helichrysum populifolium by NMR-based metabolomic guided fractionation. Fitoterapia 2015; 103: 155–164. doi: 10.1016/j.fitote.2015.03.024
44. Mcdougall B. King PJ. Wu BW. Hostomsky Z. Reinecke MG. Robinson WE. Dicaffeoylquinic and dicaffeoyltartaric acids are selective

inhibitors of human immunodeficiency virus type 1 integrase. Antimicrobial Agents and Chemotheraphy 1998; 42(1): 140-146. doi: 10.1128/AAC.42.1.140
45. Hu WS. Hughes SH. HIV-1 reverse transcription. Cold Spring Harbor Perspectives in Medicine 2012; 2(10): 1–22. doi: 10.1101/cshperspect.a006882
46. Sluis-Cremer N. Future of nonnucleoside reverse transcriptase inhibitors. Proceedings of the National Academy Sciences of the United States of America 2018; 115(4): 637–638. doi: 10.1073/pnas.1720975115
47. Chinsembu KC. Chemical diversity and activity profiles of HIV-1 reverse transcriptase inhibitors from plants. Revista Brasileira de Farmacognnosia 2019; 29(4): 504–528. doi 10.1016/j.bjp.2018.10.006
48. Kuete V. Metuno R. Keilah PL. Tshikalange ET. Ngadjui BT. Evaluation of the genus Treculia for antimycobacterial, anti-reverse transcriptase, radical scavenging and antitumor activities. South African Journal of Botany 2010; 76(3): 530–535. doi: 10.1016/j.sajb.2010.04.005
49. Martini R. Esposito F. Corona A. Ferrarese R. Ceresola ER. Visconti L. et al. Natural Product Kuwanon-L Inhibits HIV-1 Replication through Multiple Target Binding. Chembiochem: a European Journal of Chemical Biology 2017; 18(4): 374–377. doi: 10.1002/cbic.201600592
50. Cary DC. Peterlin BM. Natural Products and HIV/AIDS. AIDS Research and Human Retroviruses 2018; 34(1): 31–38. doi: 10.1089/AID.2017.0232
51. Syahdi RR. Mun'im A. Suhartanto H. Yanuar A. Virtual screening of Indonesian herbal database as HIV-1 reverse transcriptase inhibitor. Bioinformation 2012; 8(24): 1206-1210. doi: 10.6026/97320630081206.
52. Martino VS. López P. Martinez Irujo JJ. Sanromán M. Cuevas MT. Santiago E. et al. Inhibitory effect against polymerase and ribonuclease activities of HIV-reverse transcriptase of the aqueous leaf extract of Terminalia triflora. Phytheraphy Research: PTR 2002; 16(8): 778-780. doi: 10.1002/ptr.1065.
53. Dwevedi A. Dwivedi R. Sharma YK. Exploration of Phytochemicals Found in Terminalia sp. and their Antiretroviral Activities. Pharmacognosy Reviews 2016; 10(20): 73-83. doi: 10.4103/0973-7847.194048
54. Hajimahdi Z. Zarghi A. Progress in HIV-1 integrase inhibitors: A review of their chemical structure diversity. Iranian Journal of Pharmaceutical Research 2016; 15(4): 595-628.
55. Suedee A. Tewtrakul S. Panichayupakaranant P. Anti-HIV-1 integrase activity of Mimusops elengi leaf extracts. Pharmaceutical Biology 2014; 52(1): 58–61. doi: 10.3109/13880209.2013.810649.
56. Jiang F. Chen W. Yi K. Wu Z. Si Y. Han W. et al. The evaluation of catechins that contain a galloyl moiety as potential HIV-1 integrase inhibitors. Clinical Immunology 2010; 137(3): 347-356. doi: 10.1016/j.clim.2010.08.007
57. Jiang Y. Ng TB. Liu Z. Wang C. Li N. Qiao W. et al. Immunoregulatory and anti-HIV-1 enzyme activities of antioxidant components from lotus (Nelumbo nucifera Gaertn.) rhizome. Bioscience Reports 2011; 31(5): 381–90. doi: 10.1042/BSR20100062.
58. Sanna C. Rigano D. Corona A. Piano D. Formisano C. Farci D. et al. Dual HIV-1 reverse transcriptase and integrase inhibitors from Limonium morisianum Arrigoni, an endemic species of Sardinia (Italy). Natural Product Research 2019; 33(12): 1798-1803. doi: 10.1080/14786419.2018.1434649
59. Chaniad P. Sudsai T. Septama AW. Chukaew A. Tewtrakul S. Evaluation of Anti-HIV-1 integrase and anti-inflammatory activities of compounds from betula alnoides buch-ham. Advances in Pharmacological Sciences 2019; 2573965. doi: 10.1155/2019/2573965.
60. Bunluepuech K. Tewtrakul S. Anti-HIV-1 integrase activity of Thai medicinal plants in longevity preparations. Songklanakarin Journal of Science and Technology 2011; 33(6): 693-697.
61. Nguyen VD. Nguyen HLT. Do LC. Tuan VV. Thuong PT. Phan TN. A new saponin with Anti-HIV-1 protease activity from acacia pennata. Natural Product Communications 2018; 13(4): 411-414. doi: 10.1177/1934578X1801300408
62. Supinya T. Sanan S. Sopa K. HIV-1 protease inhibitory effects of medicinal plants used as self medication by AIDS patients. Songklanakarin Journal of Science and Technology 2003; 25(2) :239-243.
63. Mengoni F. Lichtner M. Battinelli L. Marzi M. Mastroianni CM. Vullo V. et al. In vitro anti-HIV activity of oleanolic acid on infected human mononuclear cells. Planta Medica 2002; 68(2): 111-114. doi: 10.1055/s-2002-20256
64. Min BS. Jung HJ. Lee JS. Kim YH. Bok SH. Ma CM. et al. Inhibitory effect of triterpenes from Crataegus pinatifida on HIV-I protease. Planta medica 1999; 65(4): 374-375. doi: 10.1055/s-2006-960792.
65. Xu HX. Zeng FQ. Wan M. Sim KY. Anti-HIV triterpene acids from Geum japonicum. Journal of Natural Products 1996; 59(7): 643-645. doi: 10.1021/np960165e.
66. Sillapachaiyaporn C. Nilkhet S. Ung AT. Chuchawankul S. Anti-HIV-1 protease activity of the crude extracts and isolated compounds from Auricularia polytricha. BMC Complementary and Alternative Medicine 2019; 19(1): 1-11. doi: 10.1186/s12906-019-2766-3
67. Kehinde I. Ramharack P. Nlooto M. Gordon M. The pharmacokinetic properties of HIV-1 protease inhibitors: A computational perspective on herbal phytochemicals. Heliyon 2019; 5(10): e02565. doi: 10.1016/j.heliyon.2019.e02565
68. Vlietinck AJ. Vanden B. Can Ethnopharmacology contribute to the development of antiviral drugs?. Journal of Ethnopharmacology 1991; 32(1-2): 141-153. doi: 10.1016/0378-8741(91)90112-q.
69. Cowan M. Plant products as antimicrobial agent. Clinical Microbiology Reviews 1999; 12(4): 564–582. doi: 10.1128/CMR.12.4.564.
70. Esimone C. Grunwald T. Wildner O. Nchinda G. Tippler B. Proksch P. et al. In vitro Pharmacodynamic evaluation of antiviral medicinal plants using a vector-based assay technique. Journal of Applied Microbiology 2005; 99(6): 1346-1355. doi: 10.1111/j.1365-2672.2005.02732.x.
71. Esimone C. Omobowajo O. Sowemimo A. Proksch P. Single-cycle vector-based antiviral screening assays for high through-put evaluation of potential anti-HIV medicinal plants: a pilot study on some Nigerian herbs. Recent Progress in Medicinal Plant Research, Phytopharmacology and Therapeutic Values 2006; 19:50–60.
72. Vanden Berghe DA. Vlietinck AJ. Van Hoof L. Plant products as potential antiviral agents. Bulletin de l'Institut Pasteur 1986; 84:101-147.
73. Munro MHG. Luibrand RT. Blunt JW. Bio Organic Marine Chemistry. Berlin: Springer Verlag. 1987.

paper

ORIGINALITY REPORT

21%	14%	19%	5%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.ncbi.nlm.nih.gov Internet Source	2%
2	eprints.utar.edu.my Internet Source	1%
3	Pulok K. Mukherjee. "Antiviral Evaluation of Herbal Drugs", Elsevier BV, 2019 Publication	1%
4	academicjournals.org Internet Source	1%
5	www.mdpi.com Internet Source	1%
6	Kazhila C. Chinsembu. "Chemical diversity and activity profiles of HIV-1 reverse transcriptase inhibitors from plants", Revista Brasileira de Farmacognosia, 2019 Publication	1%
7	Koesnoto Soepranianondo, Dhandy Koesoemo Wardhana, Budiarto, Diyantoro. "Analysis of bacterial contamination and antibiotic residue of beef meat from city	1%

slaughterhouses in East Java Province, Indonesia", Veterinary World, 2019
Publication

8	Joy Mondal, Debprasad Chattopadhyay, Keshab C. Mandal. "Anti-herpes virus agents", Elsevier BV, 2023 Publication	1 %
9	Submitted to Universitas Airlangga Student Paper	1 %
10	Márcio Viana Ramos, Cléverson Diniz Teixeira Freitas, Francimauro Sousa Morais, Erika Prado et al. "Plant latex and latex-borne defense", Elsevier BV, 2020 Publication	1 %
11	Submitted to Universitas Indonesia Student Paper	1 %
12	Van-Dung Nguyen, Hong-Loan Thi Nguyen, Linh-Chi Do, Vu Van Tuan, Phuong Thien Thuong, Tuan-Nghia Phan. " A New Saponin with Anti-HIV-1 Protease Activity from ", Natural Product Communications, 2018 Publication	1 %
13	bmccomplementmedtherapies.biomedcentral.com Internet Source	1 %
14	researchspace.ukzn.ac.za Internet Source	1 %

15	worldwidescience.org Internet Source	1 %
16	www.science.gov Internet Source	1 %
17	www.tandfonline.com Internet Source	1 %
18	Cagno, Valeria, Civra, Andrea et al. "Ficus religiosa L. bark extracts inhibit human rhinovirus and respiratory syncytial virus infection in vitro", 2015 Internet Source	<1 %
19	Submitted to Higher Education Commission Pakistan Student Paper	<1 %
20	epdf.tips Internet Source	<1 %
21	www.lib.kobe-u.ac.jp Internet Source	<1 %
22	Fardet, A.. "Lipotropic capacity of raw plant-based foods: A new index that reflects their lipotrope density profile", Journal of Food Composition and Analysis, 201111 Publication	<1 %
23	ihi.eprints.org Internet Source	<1 %

24	Yancui Huang, Di Xiao, Britt M. Burton-Freeman, Indika Edirisinghe. "Chemical Changes of Bioactive Phytochemicals during Thermal Processing", Elsevier BV, 2016 Publication	<1 %
25	Carlos Cruchaga, Elena Anso, María Font, VirginiaS. Martino, Ana Rouzaut, JuanJ. Martinez-Irujo. "A new strategy to inhibit the excision reaction catalysed by HIV-1 reverse transcriptase: compounds that compete with the template–primer", Biochemical Journal, 2007 Publication	<1 %
26	Tatiana Matveeva, Galina Khafizova, Sofia Sokornova. "In Search of Herbal Anti-SARS-Cov2 Compounds", Frontiers in Plant Science, 2020 Publication	<1 %
27	Yoichi Nakao, Nobuhiro Fusetani. "Enzyme Inhibitors from Marine Invertebrates", Journal of Natural Products, 2007 Publication	<1 %
28	Amit Kar, Ananya Das Mahapatra, Barun Das Gupta, Debprasad Chattopadhyay. "Validation of antiviral potential of herbal ethnomedicine", Elsevier BV, 2022 Publication	<1 %

29	Gerhard Prinsloo, Cynthia K. Marokane, Renée A. Street. "Anti-HIV activity of southern African plants: Current developments, phytochemistry and future research", Journal of Ethnopharmacology, 2018 Publication	<1 %
30	Zeinab T. Shakour, Mohamed A. Farag. "Diverse host-associated fungal systems as a dynamic source of novel bioactive anthraquinones in drug discovery: current status and future perspectives", Journal of Advanced Research, 2021 Publication	<1 %
31	Submitted to iGroup Student Paper	<1 %
32	Jakaphun Julsrigival, Panee Sirisa-ard, Sarinya Julsrigival, Nararat Akarchariya. "Antiviral medicinal plants found in Lanna traditional medicine", Chinese Herbal Medicines, 2021 Publication	<1 %
33	Yun Bin Han, Wei Bai, Chun Xia Ding, Jie Liang, Shao-Hua Wu, Ren Xiang Tan. "Intertwined Biosynthesis of Skyrin and Rugulosin A Underlies the Formation of Cage-Structured Bisanthraquinones", Journal of the American Chemical Society, 2021 Publication	<1 %

34	ir-library.egerton.ac.ke Internet Source	<1 %
35	lirias.kuleuven.be Internet Source	<1 %
36	mdpi.com Internet Source	<1 %
37	www.hindawi.com Internet Source	<1 %
38	A. Suedee, S. Tewtrakul, P. Panichayupakaranant. " Anti-HIV-1 integrase activity of leaf extracts ", Pharmaceutical Biology, 2013 Publication	<1 %
39	Chanin Sillapachaiyaporn, Sunita Nilkhet, Alison T. Ung, Siriporn Chuchawankul. "Anti-HIV-1 protease activity of the crude extracts and isolated compounds from Auricularia polytricha", BMC Complementary and Alternative Medicine, 2019 Publication	<1 %
40	Edible Medicinal and Non Medicinal Plants, 2014. Publication	<1 %
41	Kingkan Bunluepuech, Teeratad Sudsai, Chatchai Wattanapiromsakul, Supinya Tewtrakul. " Inhibition on HIV-1 Integrase	<1 %

Activity and Nitric Oxide Production of Compounds from ", Natural Product Communications, 2011
Publication

42	T. K. Lim. "Edible Medicinal And Non Medicinal Plants", Springer Nature, 2012 Publication	<1 %

Exclude quotes	On	Exclude matches	< 5 words
Exclude bibliography	On		