Advances in Traditional Medicine (2023) 23:953–984
https://doi.org/10.1007/s13596-022-00646-2

REVIEW

A search for potential anti-HIV phytoconstituents from the natural product repository

Dharmraj V. Pathak[1] · Sneha R. Sagar[1] · Hardik G. Bhatt[2] · Paresh K. Patel[1,2]

Received: 24 December 2021 / Accepted: 15 April 2022 / Published online: 14 May 2022
© The Author(s), under exclusive licence to Institute of Korean Medicine, Kyung Hee University 2022

Abstract

A chronic, life threatening and immuno-suppressing malady caused by Human immunodeficiency virus (HIV) is formally known as Acquired Immune Deficiency Syndrome (AIDS). Currently, combinations of several anti-retroviral drugs are being used for the management of HIV infection. These drugs possess certain limitations and hence researchers across the globe are striving to explore treatment methodologies based on medicinal plants of natural origin in order to develop safe and effective treatment. In this review, various medicinal plants are categorized on the basis of target of action namely Reverse transcriptase enzyme, Protease enzyme, Integrase enzyme, cell fusion, CC chemokine receptor 5 (CCR5) CXC chemokine receptor 4 (CXCR4). Medicinal plants exhibiting multi-targeted activities against various targets of HIV are also reviewed. Detail description of medicinal plants with their habitat, common names, category of systems of medicines, phytoconstituents and their biological activities in terms of relative % inhibition or IC_{50} or EC_{50} are provided in this review. Anti-HIV benefits of these plants are observed due to phytoconstituents like terpenoids, tannins, alkaloids, polyphenols, coumarins, flavonoids, etc. In order to gain the structural knowledge for future developments of anti-HIV leads, ligand based pharmacophore was generated using phytoconstituents mentioned in this review. Structural modifications of these phytoconstituents on hydrophobic, donor and acceptor regions are beneficial for the potent anti-HIV activity. In conclusion, this study may prove to be a stepping stone towards the use of herbal medicinal plants for the management of HIV/AIDS and may aspire researchers to look for new treatment options from the natural sources.

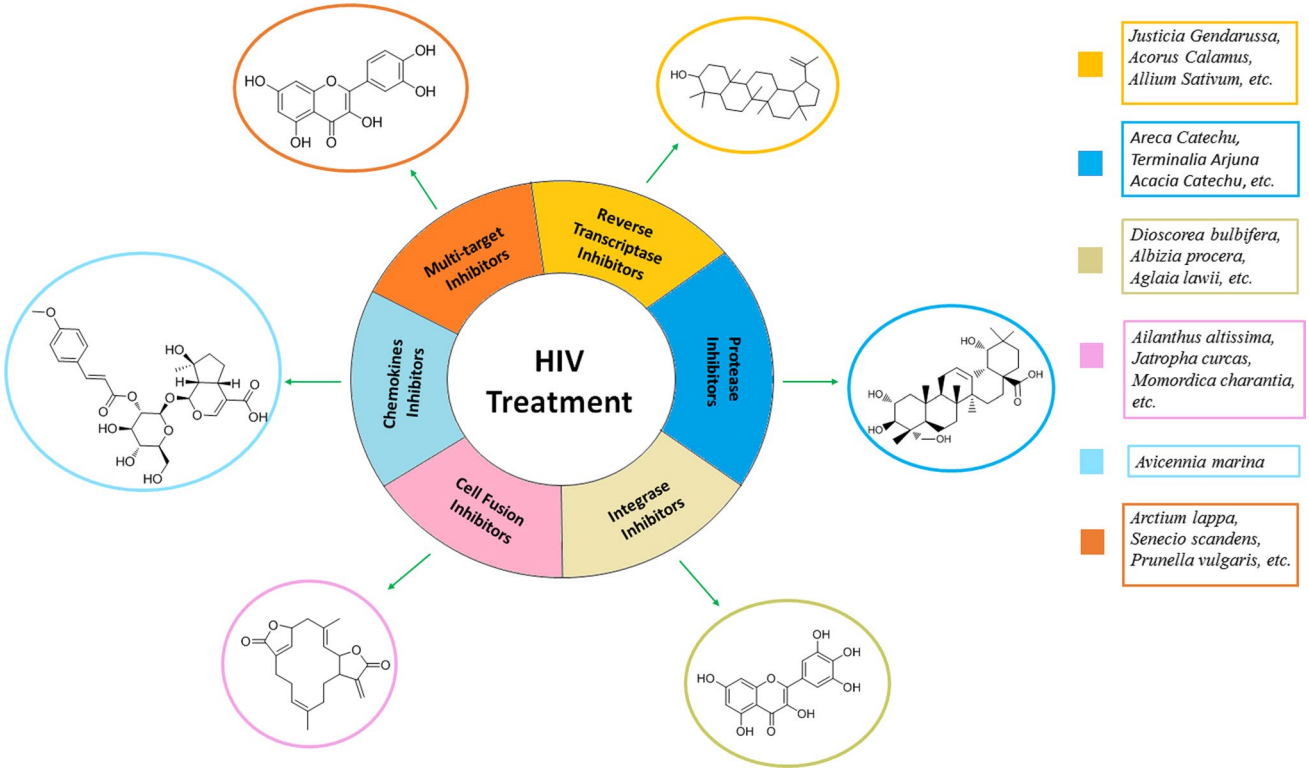
Sneha R. Sagar: Equal first author.

✉ Paresh K. Patel
pareshpharmacist@gmail.com

[1] Department of Pharmaceutical Chemistry, L.J. Institute of Pharmacy, L J University, L. J. Campus, SG Road, Ahmedabad 382 210, India

[2] Department of Pharmaceutical Chemistry, Institute of Pharmacy, Nirma University, Ahmedabad 382 481, India

Graphical abstract



Keywords HIV · AIDS · Phytoconstituents · Reverse transcriptase · Protease · Integrase · Chemokines

Abbreviations

HIV	Human immunodeficiency virus
AIDS	Acquired immune deficiency syndrome
RT	Reverse transcriptase
PR	Protease
IN	Integrase
CCR5	CC chemokine receptor 5
CXCR4	Chemokine receptor 4 (CXCR4)
% IR	Relative percent inhibition

Introduction

Acquired immunodeficiency syndrome (AIDS) is very severe and life threatening syndrome caused by Human immunodeficiency virus (HIV) (Pironti et al. 2014). HIV is responsible for declining the immunity which leads to various other secondary infection including TB, pneumonia, Herpes etc. (Rodriguez-Penney et al. 2013). HIV-I and HIV-II are two different strains of HIV virus but HIV-I is very common and affected large number of people while HIV-II is restricted to African countries (Degroote et al. 2014). HIV is commonly spread by blood transfusion and sexual transmission (Moore et al. 2014). As per WHO, Asian and African countries have maximum number of patients suffering from AIDS (Group W–H 2003). According to United Nations report, there are around 40 million patients who are living with HIV. A total number of 30 million people have died because of AIDS since its epidemic (https://aidsinfo.unaids.org/). Diagnosis of the HIV virus in the blood is usually done by viral RNA load (Hamarsheh 2020). The infection is associated with an acute symptomatic period that includes fever, general malaise, lymphadenopathy, rash, myalgia and severe consequences like meningitis (Hoenigl et al. 2016). The severity of symptoms is associated with the level of viral load and dependent on host and viral genotype (Basavaraj et al. 2010). During acute infection, higher amount of HIV RNA is present in plasma (Simon et al. 2006). HIV is difficult to diminish completely when it establishes a quiescent or latent infection within the memory CD4 + T cells because of continuous initiation of replication as HIV DNA integrated into host chromatin (Levy et al. 1996). A life cycle of HIV virus requires function of three enzymes including HIV protease, HIV reverse transcriptase and HIV integrase (Kirchhoff 2013; Boireau et al. 2007). HIV reverse transcriptase is responsible to convert single

stranded RNA to double stranded DNA (Cihlar and Ray 2010; Vernekar et al. 2015). HIV protease accounts for formation of functional protein from large polypeptide chain (Patel and Bhatt 2020; Ghosh et al. 2016; Xu et al. 2019). The integration of HIV virus into human genome is carried out by HIV integrase enzyme (Bhatt et al. 2014a; Patel et al. 2016). CXCR4 (C-X-C Motif Chemokine Receptor 4), CCR5 (C–C chemokine receptor type 5) and fusion inhibitors are the other emerging targets to treat HIV apart from three enzymes (Cagigi et al. 2008). Life cycle of HIV replication is depicted in Fig. 1.

The current treatment of AIDS is antiretroviral therapy (ART), comprises of combination therapy of reverse transcriptase inhibitor with protease or integrase inhibitor (Pelay-Gimeno et al. 2015). All these enzymes as well as receptors have been targeted and repressed by many drugs in last three decades but they have many problems like resistance and severe side effects (Bartlett and Shao 2009). Natural phytoconstituents are alternatives for the treatment of many diseases. There are various herbal drugs which have been used in diseases like digoxin in treatment of congestive heart failure, reserpine as antihypertensive, vincristine as antineoplastic, and artemisinin as antimalarial. Natural phytoconstituents do not have problems of severe side effects and drug resistance. Various phytoconstituents identified in recent years have shown different pharmacological properties. Thus, this review focuses on natural phytoconstituents with effective anti-HIV properties and the promising phytoconstituents were classified based on their mechanism of action (Yadav et al. 2017).

In this review, a complete survey of the tropical medicinal plants with their anti-HIV benefits are reviewed based on the mechanism of action. Medicinal plants are classified as Reverse transcriptase (RT) inhibitors, Protease (PR) inhibitors, Integrase (IN) inhibitors, cell fusion inhibitors, CC chemokine receptor 5 (CCR5) and CXC chemokine receptor 4 (CXCR4) inhibitors and multi-targeted acting medicinal plants. Moreover, phytoconstituents and biological activity of all the plants have been incorporated. Authentic sources of information were taken for resolving taxonomy, plant distribution and other related information (https://indiabiodiversity.org/; https://eol.org/). Scientific articles from the year 1970 to 2021 were taken from the electronic databases i.e., Pubmed, Science Direct, Google Scholar, Web of Science

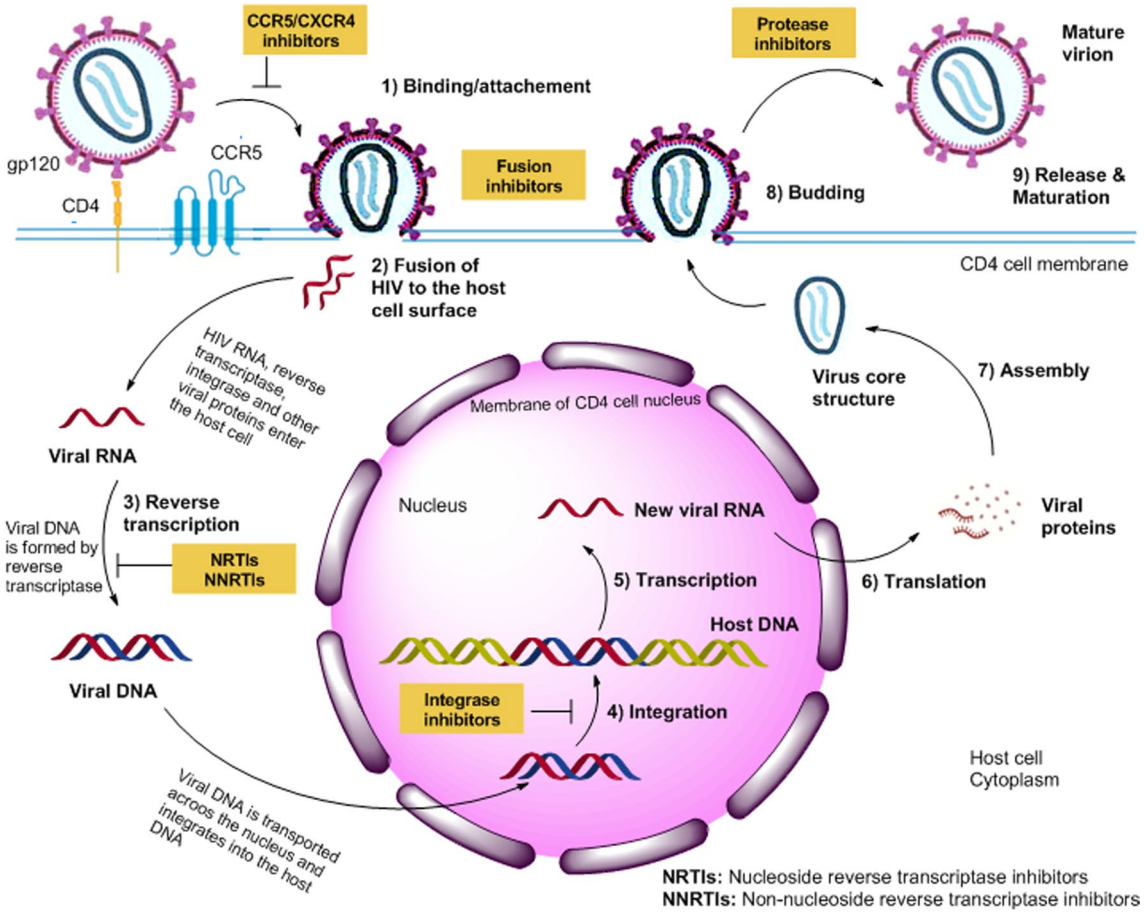


Fig. 1 Life cycle of HIV virus

and Scopus. The terms used for this review included anti-HIV agents, all the botanical names and synonyms of the species, phytoconstituents present in each plant, and biological activity of each medicinal plant.

Tropical medicinal plants used against HIV

Reverse transcriptase (RT) inhibitors

Reverse transcriptase inhibitors or Anti-RT drugs act on reverse transcription of the HIV by inhibiting reverse transcriptase enzyme. These drugs inhibit the formation of viral DNA and restrict the expansion of the HIV throughout the body (Maartens et al. 2014). Indian herbal plants namely *Justicia Gendarussa Burm.F., Acorus Calamus L., Allium Sativum L., Hemidesmus Indicus (L.) R. Br, Canna Indica L., Anogeissus Acuminata (Roxb. ex DC.) Guill., Perr. & A. Rich., Swertia Franchetiana, Vitex Trifolia L., Artocarpus Heterophyllus Lam.,* and *Plumbago Indica L.* are reported to have anti-RT benefits. The active chemical constituents of these medicinal plants are summarized in this review.

Justicia Gendarussa Burm.F.

Justicia Gendarussa is native to tropical Asia. In India, it is found in Kerala, Tamil Nadu, Assam and Maharashtra. It is used in several systems of medicine such as Folk medicine, Ayurveda, Sidhha, Unani and Traditional Chinese medicine. It has several common names in India such as Water Willow, Kala Bashimb, Nili Nargand, Indrani and Kapika (https://indiabiodiversity.org/). Aerial part of this plant has RT inhibitory activity for treating HIV/AIDS. Crude extract of this plant exhibited potent HIV-1 RT inhibition activity in i*n vitro* studies (Woradulayapinij et al. 2005). Crude extract of aerial part contains mixture of phytosterol and flavonoids such as β-sitosterol, β-sitosterol-β-D-glycoside and Aromadendrin. Crude water extract of *Justicia Gendurussa* showed anti-RT activity by acting on reverse transcription of the viral RNA genome at the concentration of 200 µg/ml with inhibition ratio (relative % inhibition [IR]) higher than 90% (Maartens et al. 2014; Woradulayapinij et al. 2005).

Acorus Calamus L.

Acorus calamus L. is obtained from the north temperate hemisphere and tropical Asia. In India, it is distributed mainly in Kerala, Punjab, and Assam. It is used in several systems of medicine such as Folk medicine, Ayurveda, Sidhha, Unani, Traditional Chinese medicine, Sowa-Rigpa, and modern medicine. It is also known as sweet root and Gorbach. Rhizome of this plant showed activity against HIV/AIDS (Salehi et al. 2018). In vitro studies of this plant revealed that crude hexane extract has very strong HIV-1 RT inhibition activity with IC_{50} of 33.96 µg/ml (Silprasit et al. 2011). The crude rhizome part contains alkaloids, flavonoids, gums, lectins, mucilage, phenols, quinone, saponins, sugars, tannins, and triterpenes (steroids).

Allium Sativum L.

Allium Sativum is commonly known as Garlic. It is native throughout India. It is used in several systems of medicine such as Folk medicine, Ayurveda, Sidhha, Unani, Homoeopathy, Traditional Chinese medicine, Sowa-Rigpa, and Modern medicine. It is reported that bulb of garlic has HIV-RT inhibitory activity (Silprasit et al. 2011). Crude hexane extract of the garlic showed > 80% relative inhibition (Silprasit et al. 2011). Crude extract of this plant contains bioactive compounds like Alliin, Allicin, (E)-ajoene, Allyl sulfide, (Z)-ajoene, and 1,2-vinyldithiin (Martins et al. 2016).

Hemidesmus Indicus (L.) R. Br

Hemidesmus Indicus is known as Indian Sarsaparilla or Anantmul. In India, it is mainly distributed in Maharashtra, Tamil Nadu, Kerala, Karnataka, Meghalaya and Assam. Roots of the *Hemidesmus Indicus* has potent HIV-RT inhibitory activity. Crude extract mainly contains various bioactive compounds such as two pentacyclic triterpenoic derivatives, Lupeol and Lupeol acetate. 2-hydroxy-4-methoxybenzaldehyde, 3-hydroxy-4-methoxybenzaldehyde, 2-hydroxy-4-methoxybenzoic acid, caffeic acid, chlorogenic acid and β- amyrin acetate can also be obtained from the crude extract. Lupeol has promising effect on RNA dependent DNA polymerase (RDDP) enzyme and RNase H function against HIV-RT with IC_{50} of > 100 µM and 11.6 µM, respectively (Esposito et al. 2017). Lupeol acetate also showed activity against RDDP and RNase H with IC_{50} of 100 µM and 63 µM, respectively. Lupeol and its acetate bind with allosteric site of the RNase H and exhibit inhibition activity. Studies on decoction of *Hemidesmus Indicus* indicated the inhibitory action against RNase H and RDDP enzyme with IC_{50} values of 3 and 7 µg/ml, respectively (Esposito et al. 2017).

Canna Indica L.

Canna Indica is known as Indian shot and canna lily. It is native throughout India, Sri Lanka and Malaysia. It is used in several systems of medicine such as Folk medicine, Ayurveda, Sidhha and Traditional Chinese medicine. *Canna Indica L.* belongs to family Cannaceae. It is reported that Rhizome of this plant has potent anti-RT activity against AIDS/HIV (Woradulayapinij et al. 2005). Crude water extract of this plant showed 92% IR at 200 µg/

ml (Woradulayapinij et al. 2005). Crude extract of Canna contains polar compounds like polyphenolics (flavonoids, tannins), triterpenoids, steroids and some sugars (Kumbhar et al. 2018).

Anogeissus Acuminata (Roxb. ex DC.) Guill., Perr. & A. Rich.

Anogeissus Acuminata is a tree of Combretaceae family (Rimando et al. 1994). It is generally known as Button tree and Dhaura. It is widely distributed in India. Chemical constituents of this plant i.e., Anolignan A and Anolignan B have potent action on the reverse transcription of retrovirus. Generally, Anolignan A and Anolignan are given in combination. HIV-1 RT IC_{50} (µg/ml) of Anolignans A and B in combination is 30–50 µg/ml and percentage inhibition is more than 90% (Rimando et al. 1994).

Swertia Franchetiana

Swertia Franchetiana is the Indian medicinal plant also known as Panicled Swertia. It belongs to Gentianaceae family. It is used in Ayurveda medicinal system. It has notable action on reverse transcriptase enzyme of HIV (Pengsuparp et al. 1995). One of the constituents, Xanthone (extracted out from the root of *Swertia Franchetiana*) showed promising anti-RT action in the reported studies. Swertifrancheside and Swertipunicoside are the active phytoconstituents of this plant. These constituents showed inhibition of reverse transcription at ED_{50} of 30.9 µg/ml and 3.0 µg/ml for Swertifrancheside and Swertipunicoside, respectively (Pengsuparp et al. 1995; Wang et al. 1994).

Vitex Trifolia L.

Vitex trifolia L. is well known as Arabian Lilac. It is cultivated in South India and Assam. It is a tree of Lamiaceae family (Woradulayapinij et al. 2005). It is used in several systems of medicine such as Folk medicine, Ayurveda, Sidhha, Unani, Traditional Chinese medicine and Sowa-Rigpa. Arial part of this tree has very strong anti-RT action. Crude water extract of Vitex trifolia has 98.06% inhibition against reverse transcription at 200 µg/ml (Woradulayapinij et al. 2005). Crude extract of aerial part of this medicinal plant contains polyphenolic compounds, flavonoids, proteins, tannins, phytosterols, and saponins. Several monoterpenes along with diterpenes, dihydrosolidagenone, beta-sitosterol-3-O-glucoside, terpineol, alpha-pinene, 3,6,7-trimethylquercetagetin, hexanic and dichloromethanic can also be extracted from the stem (Suchitra and Cheriyan 2018).

Artocarpus Heterophyllus Lam.

Artocarpus Heterophyllus Lam. is generally known as Jack Fruit and it is well known as Katahal in India. This plant belongs to Moraceae family. It is obtained from Jammu and Kashmir, Himachal Pradesh, and Sikkim. *Artocarpus Heterophyllus* is used in several systems of medicine such as Folk medicine, Ayurveda, Sidhha, Unani and Traditional Chinese medicine. Crude extract of seeds of jackfruit showed very potent and strong inhibitory effect against HIV-1 RT with > 80% IR at 0.225 mg/ml (Silprasit et al. 2011). Crude extract of jackfruit seed contains protein, calcium, iron, Tiamine, carbohydrates specially starch and various phytochemicals such as phenolic compounds, flavonoids, tannins and saponins. Seeds have three phenolic acids, viz., gallilc acid, tannic acid, and ferulic acid (Ranasinghe et al. 2019).

Plumbago Indica L.

Plumbago Indica belongs to Plumbaginaceae family. It is cultivated in South East Asia. In India, it is obtained mainly from Kerala and Tamil Nadu. It is commonly known as Fire plant, Radix Plumbago, and Chitrakmool. Root of this plant is used to treat AIDS/HIV-1 (Silprasit et al. 2011). Study on the crude extract of root showed potent anti-RT action with more than 80% IR at 0.255 mg/ml (Silprasit et al. 2011). Crude extract contains napthoquinone specially plumbagin, which has greater medicinal benefits. Crude plant extract also contains some phytochemicals like palmitic acid, myricyl palmitate, plumbagic acid, lactone, ayanin, and azalenin (Dinda et al. 2019). The phytoconstituents having HIV-RT inhibitory activities are given in Table 1.

Protease inhibitors (anti-PR drugs)

Protease inhibitors or anti-PR drugs act on the formation of viral protein of the HIV by inhibiting protease enzyme (Maartens et al. 2014). Due to protease inhibition, envelop protein and other proteins cannot be formed and therefore spreading of the infection throughout the body can be controlled. Tropical herbal plants and their chemical constituents which are most active and potent reviewed below.

Areca Catechu L.

It is known as Supari and Areca palm in India. It is mainly cultivated in Arunachal Pradesh, Assam, Manipur, and Meghalaya in India. It is used in several systems of medicine such as Folk medicine, Ayurveda, Sidhha, Unani, Traditional Chinese medicine, Sowa-Rigpa, and Modern medicine (https://indiabiodiversity.org/). Seeds of the plants are reported to have activity against HIV (Kusumoto et al. 1995). Crude extract from the seeds of *Areca Catechu*

Table 1 Chemical structures of phytoconstituents having HIV reverse transcriptase inhibitory activity

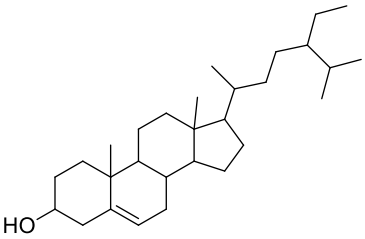
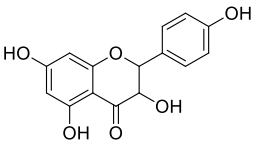
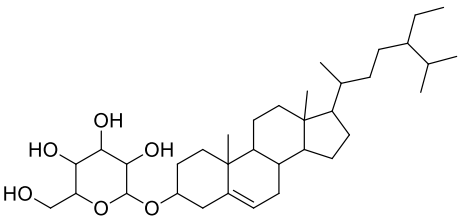
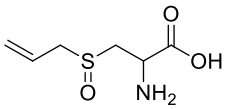
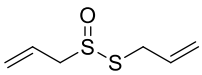
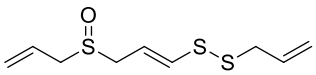
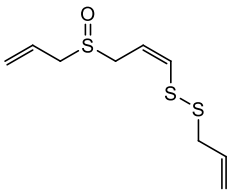
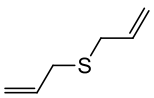
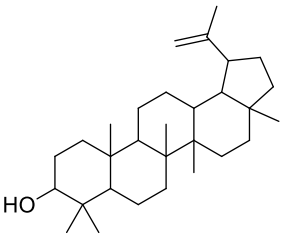
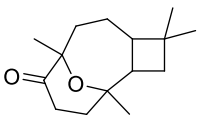
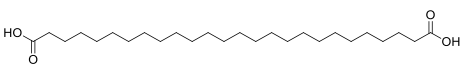
Sr.no	Phytoconstituents	Name of plant	Structure	References
1	β-sitosterol	*Justicia Gendurussa*		Maartens et al. (2014), Woradulayapinij et al. (2005)
2	Aromadendrin	*Justicia Gendurussa*		Maartens et al. (2014), Woradulayapinij et al. (2005)
3	β-Sitosterol-β-D-glycoside	*Justicia Gendurussa*		Maartens et al. (2014), Woradulayapinij et al. (2005)
4	Alliin	*Allium Sativum L*		Silprasit et al. (2011), Martins et al. (2016)
5	Allicin	*Allium Sativum L*		Silprasit et al. (2011), Martins et al. (2016)
6	(E)-ajoene	*Allium Sativum L*		Silprasit et al. (2011), Martins et al. (2016)
7	(Z)-ajoene	*Allium Sativum L*		Silprasit et al. (2011), Martins et al. (2016)
8	Diallylsulfane	*Allium Sativum L*		Silprasit et al. (2011), Martins et al. (2016)
9	Lupeol	*Hemidesmus Indicus*		Esposito et al. (2017)
10	3, 7-Epoxycaryophyllan-6-one	*Canna Indica*		Woradulayapinij et al. (2005), Kumbhar et al. (2018)
11	Hexacosanedioic acid	*Plumbago Indica*		Silprasit et al. (2011), Dinda et al. (2019)

Table 1 (continued)

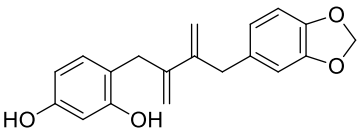
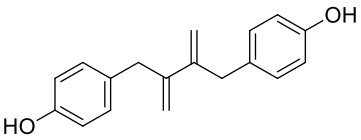
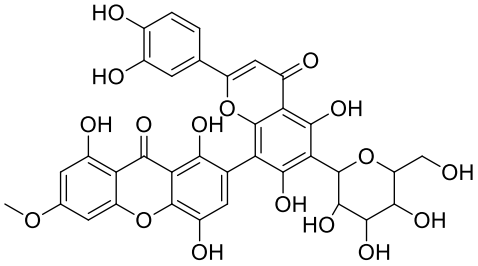
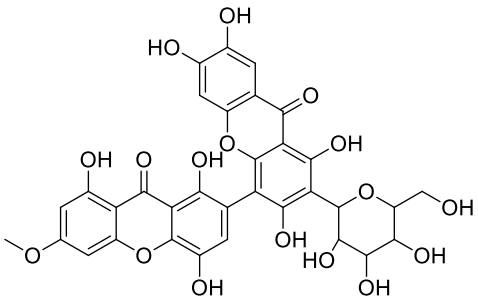
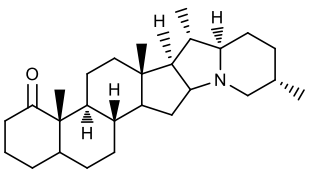
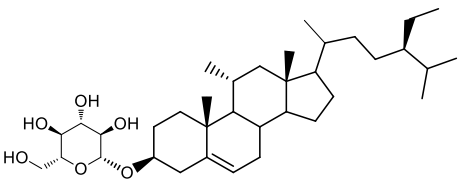
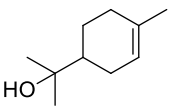
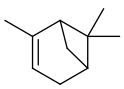
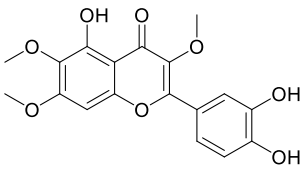
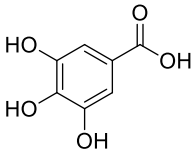
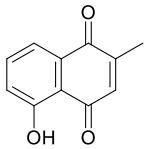
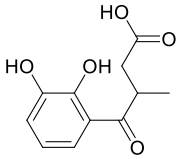
Sr.no	Phytoconstituents	Name of plant	Structure	References
12	Anolignan A	*Anogeissus Acuminata*		Rimando et al. (1994)
13	Anolignan B	*Anogeissus Acuminata*		Rimando et al. (1994)
14	Ertifrancheside	*Swertia Franchetiana*		Pengsuparp et al. (1995), Wang et al. (1994)
15	Swertipuicoside	*Swertia Franchetiana*		Pengsuparp et al. (1995, Wang et al. (1994)
16	Dihydrosolidagenone	*Vitex Trifolia L*		Woradulayapinij et al. (2005), Suchitra and Cheriyan (2018)
17	β-sitosterol-3-O-glucoside	*Vitex Trifolia L*		Woradulayapinij et al. (2005), Suchitra and Cheriyan (2018)
18	Terpineol	*Vitex Trifolia L*		Woradulayapinij et al. (2005), Suchitra and Cheriyan (2018)
19	α-pinene	*Vitex Trifolia L*		Woradulayapinij et al. (2005), Suchitra and Cheriyan (2018)
20	3,6,7-trimethylquercetagetin	*Vitex Trifolia L*		Woradulayapinij et al. (2005), Suchitra and Cheriyan (2018)

Table 1 (continued)

Sr.no	Phytoconstituents	Name of plant	Structure	References
21	Gallilc acid	*Artocarpus Heterophyllus Lam*		Silprasit et al. (2011), Ranasinghe et al. (2019)
22	Plumbagin	*Plumbago Indica*		Silprasit et al. (2011), Dinda et al. (2019)
23	Plumbagic acid	*Plumbago Indica*		Silprasit et al. (2011), Dinda et al. (2019)

showed very potent HIV-PR inhibitory activity (Kusumoto et al. 1995). Water and methanol crude extracts also exhibited inhibition of protease enzyme. % inhibition of protease enzyme for water and methanol crude extract was found to be 71.5 ± 1.5% and 84.1 ± 0.7%, respectively at the concentration of 0.2 mg/mL (Kusumoto et al. 1995). Crude extract of the plant contains mainly three areca tannins viz. Procyanidin B1, Arecatannin A1 and Arecatannin B1 (Pelay-Gimeno et al. 2015). (+)-Catechin, (−)-Epicatechin, (−)-Epicatechin gallate and (−)-Epigallocatechin gallate are also found in the crude extract of the plant. Arecatannin A1 and B1 both showed inhibition of the protease enzyme at an IC_{50} of 0.5 mM (Kusumoto et al. 1995).

Terminalia Arjuna

Terminalia Arjuna belongs to Combretaceae family and it is better known as Arjun tree in India. It is easily available in India and Sri Lanka. It is used in the several systems of medicine such as Folk medicine, Ayurveda, Sidhha, Unani, Traditional Chinese medicine, and Sowa-Rigpa. HIV-PR inhibitory activity is reported for the stem bark of the Arjun tree. Crude extract of the stem bark is used to treat HIV (Kusumoto et al. 1995; Xu et al. 1996; Sabde et al. 2011). Water crude extract and methanol crude extract of the Arjun stem bark showed HIV-PR inhibition with 80% and 83%, respectively at the concentration of 0.2 mg/ml (Kusumoto et al. 1995; Xu et al. 1996). Crude extract of the Arjun stem bark contains terpenes such as Triterpenoids, and Ursane triterpenoids. It also contains other phytochemicals like Glycosides, Flavonoids, Phenolics, and Tannins (Sabde et al. 2011; Amalraj and Gopi 2017). Among all the phytoconstituents, terpenes have significant action on the HIV-PR (Amalraj and Gopi 2017). Crude extract of the Arjun stem bark contains several Triterpenes like Arjunin (Amalraj and Gopi 2017; Row et al. 1970), Arjunic acid (Amalraj and Gopi 2017; Row et al. 1970), Arjungenin (Amalraj and Gopi 2017; Honda et al. 1976; Singh et al. 2002a, 2002b), Terminic acid (Amalraj and Gopi 2017; Anjaneyulu and Prasad 1983), Terminoltin (Amalraj and Gopi 2017; Singh et al. 1995) and Arjunolic acid (Amalraj and Gopi 2017; Singh et al. 2002a, 2002b; Wang et al. 2010). Ursane triterpenoids namely, 2α,3β-dihydroyurs-12,18-oic acid 28-O-β-D-glucopyranosyl ester, 2α,3β,23-trihydroxyurs-12,18-dien-28-oic acid 28-O-β-glucopyranosyl ester, Qudranoside VIII, Kajiichigoside F1; 2α,3β,23-trihydroxyurs-23-trihydroxyurs-12,19-dien-28-oic acid 28-O-β-D-glucopyranosyl ester type of phytochemicals are also present in the extract (Amalraj and Gopi 2017; Singh et al. 2002b).

Acacia Catechu

Acacia catechu is commonly known as Catechu, Cachou and Black cutch (Modi et al. 2013; Li et al. 2010). It is mainly cultivated in East, Central, South and North Indian states such as Tamil Nadu, Karnataka, Maharashtra, Andhra Pradesh, Gujarat, Madhya Pradesh, Uttar Pradesh and Rajasthan (Modi et al. 2013). It is a tree of Fabaceae family. It is used in the several systems of medicine such as Folk medicine, Ayurveda, Sidhha, Unani and Traditional Chinese medicine. Several compounds have been isolated from *Acacia Catechu* such as 4-hydroxybenzoic acid, Kaempferol, Quercetin, 3, 4', 7-trihydroxyl-3′,5-dimethoxyflavone, Catechin, Rutin, Isorhamnetin, Epicatechin, Afzelechin, Epiafzelechin, Mesquitol, Ophioglonin, Aromadendrin and Phenol. Among these chemical constituents, Catechin, Rutin and Isorhamnetin have antioxidant property by scavenging free radicals (Modi et al. 2013; Li et al. 2010; Li et al. 2011).

Flavonoids of this plant have promising anti-inflammatory activity and immunomodulatory activity (Modi et al. 2013; Li et al. 2011). Resin of the stem bark has significant inhibitory activity of HIV-PR. Studies reported that crude n-butanol fraction of this plant showed very potent activity against HIV-PR with an IC_{50} of 12.9 µg/ml at the concentration of 50 µg/ml (Modi et al. 2013). Catechin and Epicatechin showed significant protease inhibitory activity at an IC_{50} of 0.60 µg/ml and CC_{50} of 950 µg/ml (Modi et al. 2013).

Acacia Nilotica (L.)

Acacia Nilotica is well distributed in India and mostly known as Babul. Babul tree is also known as Gum Arabic tree. This plant belongs to family Fabaceae (Hussein et al. 1999). Studies on HIV-PR are reported for the stem bark and pods of this plant. Methanol crude extract of *Nilotica* pods exhibited activity against HIV-PR with an IC_{50} of 57 µg/ml. Water crude extract of *Nilotica* pods showed HIV-PR inhibition with an IC_{50} of 48 µg/ml. Tannins are present in the plant extract which are having promising biological activities along with HIV-PR inhibition activity (Hussein et al. 1999). Crude extract of this plant also contains terpenoids, tannins, alkaloids, saponins and glycosides (Hegde et al. 2017).

Saraca Indica

Saraca Indica is well known as Ashok tree and Asopalva. This tree belongs to Fabaceae family. The Ashok tree is mainly cultivated in Kerala, Tamil Nadu, and Gujarat. Stem bark of Ashok tree is reported for the activity against HIV-PR (Kusumoto et al. 1995). Crude aqueous extract of this plant has very strong activity against HIV-PR with 84% inhibition at the concentration of 0.2 mg/ml (Kusumoto et al. 1995). Crude extract of Ashoka contains main chemical constituents such as (+)-Catechin (CAT), (−)-Epicatechin (EPI), Procyanidin B-2, 11'-deoxyprocyanidin B4, and Leucocyanidin (Tandon and Yadav 2017; Senapati et al. 2012; Srivastava et al. 1988; Shirolkar et al. 2013).

Plectranthus Barbatus Andrews

Plectranthus Barbatus is a folk medicine from Lamiaceae family. It is known as Pashan Bhedi, and Patharchur. Global distribution of this plant is in India, Sri Lanka, and Tropical East Africa. Generally, it is cultivated from Tamil Nadu and Maharashtra. Leaves of this plant has promising activity against several enzymes mainly protease enzyme (Kapewangolo et al. 2013). Crude ethanolic extract of *Plectranthus Barbatus* showed dose dependent activity against HIV-PR (Kapewangolo et al. 2013). *P. Barbatus* inhibited the enzyme HIV-PR with an IC_{50} of 62.0 ± 0.2 µg/ml. Inhibition of HIV-1-PR could be attributed to some diterpenoid compounds present in this plant (Kapewangolo et al. 2013; Alasbahi and Melzig 2010a, 2010b). This plant has potential to inhibit inflammatory cytokines (Kapewangolo et al. 2013). A diterpenoid, Isoforskolin is isolated from the *Plentracthus Barbatus* leaf (Haque et al. 2015).

Punica granatum L.

Punica granatum L. is well known as pomegranate. It is cultivated throughout Assam, Kashmir, and Maharastra. It is used in several systems of medicine such as Folk medicine, Ayurveda, Sidhha, Unani, Traditional Chinese medicine, and Sowa-Rigna. This plant belongs to family Lythraceae (Kusumoto et al. 1995). Crude aqueous extract of pomegranate from the root bark showed 88% inhibition of HIV-PR at 250 µg/ml concentration (Kusumoto et al. 1995; Xu et al. 1996). Crude extract of the pomegranate root bark (pericarp) contains tannins such as Gallic acid, Granatin A, Corilagin and Ellagic acid. The Pomegranate fruit contains Ellagitanin and Ellagic acid (Alasbahi and Melzig 2010b).

Adansonia Digitata L.

Adansonia Digitata L. has several common names in India such as Gorakh Imli, Brahmamlika, Bottle tree and Dead rat tree. It is cultivated mainly in Maharashtra and Gujarat. It is used in several systems of medicine such as Folk medicine, Ayurveda, Sidhha, and Unani. This plant belongs to Malvaceae family. It is one of the largest and reportedly longest living species of the world (Sharma and Rangari 2016). Leaf and fruit pulps of bottle tree have significant action against HIV-PR (Sharma and Rangari 2016). Crude ethanolic leaf extract of bottle tree showed 75% inhibition of HIV-PR at the concentration of 50 µg/ml. Importantly, Fruit pulp extract of this plant exhibited 74% inhibition of HIV-PR at the concentration of 50 µg/ml (Sharma and Rangari 2016). Crude extract contains vitamin C, sugar, potassium tartrate and calcium. Leaves of this plant are rich in phenolic compounds with several other chemical constituents such as Procyanidin, O-glycosides of Apigenin, Quercetin (Quercetin glycoside, Rutin, Quercetin pentoside, Quercetin 3-hydroxy-3-methylglutaryl-O-hexoside), Kaempferol derivatives, C-glycoside Vitexin or Isovitexin, and Aglycone quercetin (Braca et al. 2018).

Andrographis Paniculata

Andrographis Paniculata belongs to family Acanthaceae. It is well known as Andrographis and Kalmegh. It is cultivated in India and Sri Lanka. In India, it is cultivated in Assam, Kerala, Gujarat, Madhya Pradesh, and Odisha. Aerial part of Kalmegh reported to have significant inhibition of HIV-PR

(Niranjan Reddy et al. 2005). Novel Bis-andrographolide ether, Andrographolide, 14-deoxy-11,12-didehydroandrographolide, Andrograpanin, 14-deoxyandrographolide, (±)-5-hydroxy-7,8-dimethoxyflavanone, and 5-hydroxy-7,8-dimethoxyflavone have been isolated from the aerial parts of *Andrographis Paniculata* and their structures were established by spectral data (Niranjan Reddy et al. 2005). Among these compounds, Andrographolide (EC_{50} = 49.0 µg/mL) and 14-deoxy-11,12-didehydroandrographolide (EC_{50} = 56.8 µg/mL) showed significant anti-HIV activity (Niranjan Reddy et al. 2005). A comprehensive list of phytoconstituents having HIV-PR inhibitory activities are given in Table 2.

Integrase inhibitors (anti-IN drugs)

HIV-IN inhibitors or anti-IN drugs inhibit the enzyme integrase. IN inhibitors act on HIV double stranded DNA and inhibit the formation of proviral RNA in cell nucleus (Maartens et al. 2014). By this mechanism, IN inhibitors prevent incorporation of HIV into host genome. Indian herbal plants and their chemical constituents with HIV-IN inhibitory activities are reviewed below.

Dioscorea bulbifera L.

Dioscorea bulbifera L. belongs to family Dioscoreaceae. It is also known as Air Potato and Ratalu. It is used in several systems of medicine such as Folk medicine, Ayurveda, Sidhha, Unani, Traditional Chinese medicine and Sowa-Rigpa. It is globally distributed on Paleotropics and mainly cultivated in Maharashtra, Karnataka, Kerala, Tamil Nadu, etc. It is the traditional Indian and Chinese medicinal plant (Chaniad et al. 2016). It is used for sore throat, gastric cancer, carcinoma of the rectum and many other diseases. Reported literature suggested that air potato has inhibitory action against HIV-IN (Chaniad et al. 2016). Air Potato contains Allantoin, 2,4,30,50-tetrahydroxybibenzyl, 2,4,6,7-tetrahydroxy-9,10-dihydrophenanthrene, Myricetin, 5,7,40-trihydroxy-2-styrylchromone, Quercetin-3-O-β-D-glucopyranoside, and Quercetin-3-O-β-D-galactopyranoside. Among these compounds, Myricetin has the most potent inhibitory action with IC_{50} value of 3.15 µM (Chaniad et al. 2016). 2,4,6,7-tetrahydroxy-9,10-dihydrophenanthrene, Quercetin-3-O-β-D-glucopyranoside, and Quercetin-3-O-β-D-galactopyranoside showed HIV-IN inhibition with IC_{50} of 14.20 µM, 19.39 µM and 21.80 µM, respectively (Chaniad et al. 2016).

Albizia procera (Roxb.) Benth.

Albizia procera belongs to the family Fabaceae and it is also known as White siris tree. It is used in several systems of medicine such as Folk medicine, Ayurveda, Sidhha, and Unani. It is easily available in Andaman & Nicobar Island, Assam, Madhya Pradesh, Meghalaya, Odisha, Uttar Pradesh, etc. Bark of white siris tree has promising HIV-IN inhibitory activity (Bunluepuech and Tewtrakul* 2011). Crude water extract of bark showed potent inhibitory activity against HIV-IN with the IC_{50} of 5.9 µg/ml. HIV-IN inhibition was reported for the two main phytoconsituents, (+)-Catechin and Protocatechuic acid of the bark extract (Bunluepuech and Tewtrakul* 2011; Panthong et al. 2015).

Aglaia lawii (Wight) C.J. Saldanha

Aglaia lawii is also known as Karakil. This plant belongs to Meliaceae family. In India, it is mainly cultivated in Kerala and Maharashtra. Leaves of this plant is reported for HIV-IN activity. Crude extract of leaves contains several phytochemicals such as Retusin, Pachypodol, (−)-Yangambin, Pyramidatine, 24-epi-piscidinol A, Aglaiodiol, Cycloart-23E-ene-3β-25-diol, Pyramidaglain A, Pyramidaglain B, and *N*-methyl-trans-4-hydroxy-L-proline. Among these compounds, *N*-methyl-trans-4-hydroxy-L-proline has very potent anti HIV-IN effects with an IC_{50} of value 11.8 µg/ml (Puripattanavong et al. 2016).

Toddalia asiatica (L.) Lam.

Toddalia asiatica L. is known as Forest pepper and it belongs to family Rutaceae. It is used in several systems of medicine such as Folk medicine, Ayurveda, Sidhha, and Traditional Chinese Medicine. It is cultivated in Kerala, Karnataka, Tamil Nadu, and Assam. Root extract of this plant contains Benzo[c]phenanthridine alkaloids, Quinoline alkaloids, and Coumarin derivatives (Rashid et al. 1995). Among these compounds, Nitidine (quaternary benzo[c]phenanthridine alkaloid) and Magnoflorine (Aporphinoid alkaloid) showed potent anti-HIV-IN activity. Nitidine efficiently inhibited the HIV-IN at a concentration range of 1–10 µg/ml (Rashid et al. 1995). The phytoconstituents having HIV-IN inhibitory activities are given in Table 3.

Cell fusion inhibitors

HIV envelope glycoprotein (Env) comprises of gp120 and gp41subunits. Among these subunits gp120 binds to the CD4 receptor. This causes conformational changes in Env and it reveals the binding site for co-receptor (chemokine). This initiates the membrane fusion process as the fusion peptide of gp41 inserts into the target membrane, followed by six-helix bundle formation and complete membrane fusion (Wilen et al. 2012; Zaitseva et al. 2017). Some medicinal plant extracts are able to inhibit the HIV cell entry by inhibiting cell fusion. Medicinal plants targeting cell fusion are reviewed as below.

Table 2 Chemical structures of phytoconstituents having HIV protease inhibitory activity

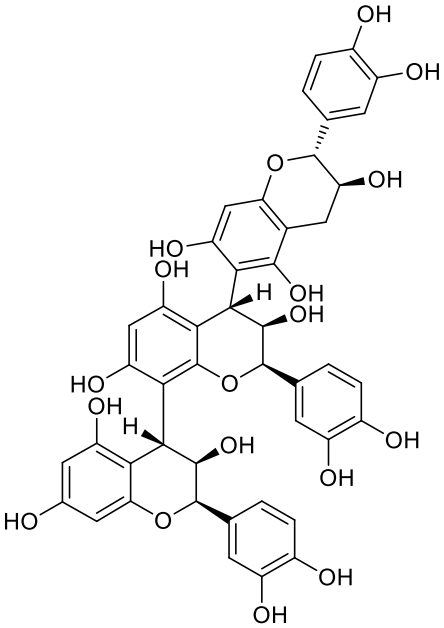
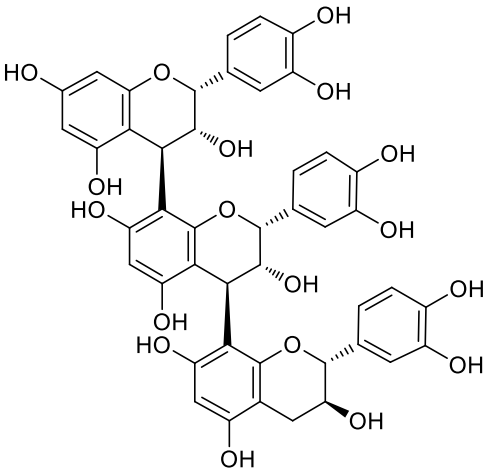
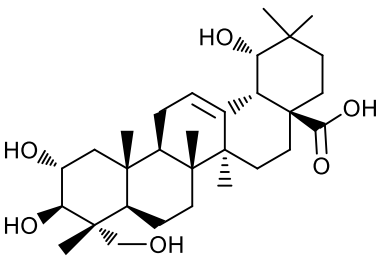
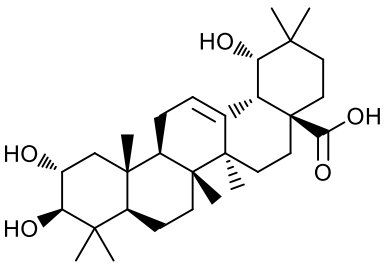
Sr.no	Phytoconstituents	Name of plant	Structure	References
1	Arecatannin B1	*Areca Catechu L*		Kusumoto et al. (1995)
2	Arecatannin A1	*Areca Catechu L*		Kusumoto et al. (1995)
3	Arjungenin	*Terminalia Arjuna*		Amalraj and Gopi (2017), Honda et al. (1976), Singh et al. (2002a), Singh et al. (2002b)
4	Arjunic Acid	*Terminalia Arjuna*		Amalraj and Gopi (2017), Row et al. (1970)

Table 2 (continued)

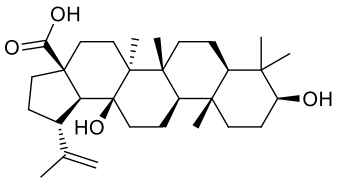
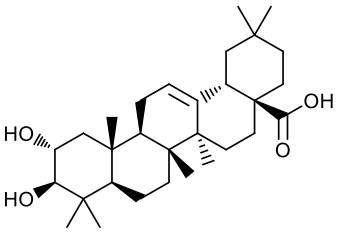
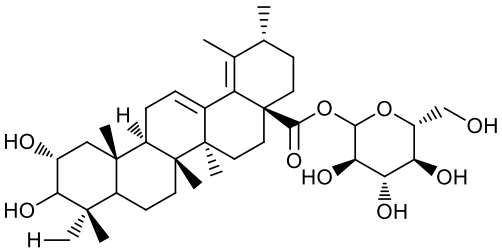
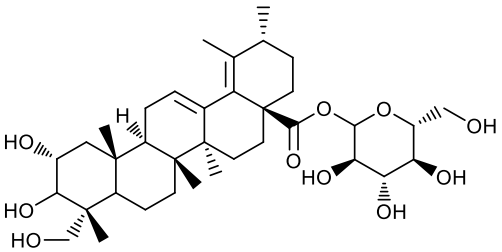
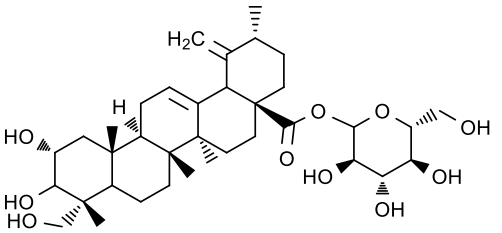
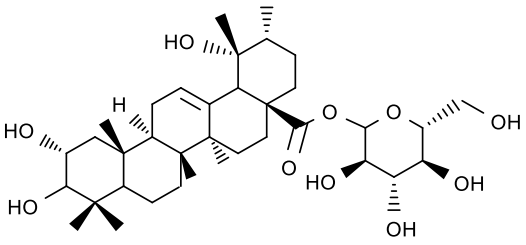
Sr.no	Phytoconstituents	Name of plant	Structure	References
5	Terminic Acid	*Terminalia Arjuna*		Amalraj and Gopi (2017), Anjaneyulu and Prasad (1983)
6	Arjunolic acid	*Terminalia Arjuna*		Amalraj and Gopi (2017), Singh et al. (2002a) Singh et al. (2002b), Wang et al. (2010)
7	2α,3β-dihydroyurs-12,18-oic acid 28-O-β-D-glucopyranosyl ester	*Terminalia Arjuna*		Amalraj and Gopi (2017), Modi et al. (2013)
8	2α,3β,23-trihydroxyurs-12,18-dien-28-oic acid 28-O-β-glucopyranosyl ester	*Terminalia Arjuna*		Amalraj and Gopi (2017), Modi et al. (2013)
9	Qudranoside VIII	*Terminalia Arjuna*		Amalraj and Gopi (2017), Modi et al. (2013)
10	Kajiichigoside F1	*Terminalia Arjuna*		Amalraj and Gopi (2017), Modi et al. (2013)

Table 2 (continued)

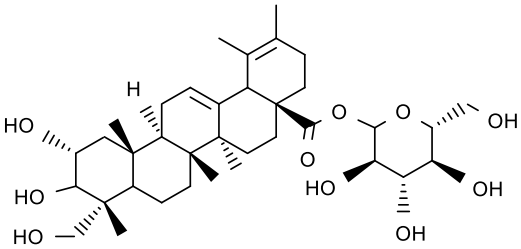
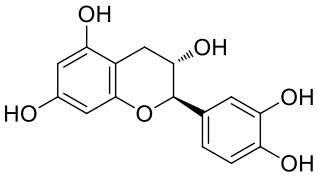
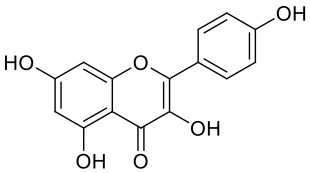
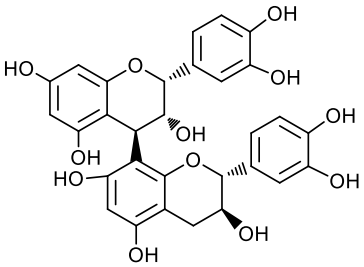
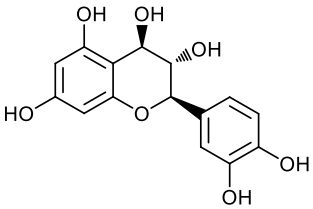
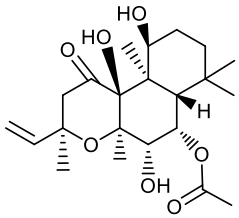
Sr.no	Phytoconstituents	Name of plant	Structure	References
11	2α,3β,23-trihydroxyurs-23-trihydroxyurs-12,19-dien-28-oic acid 28-O-β-D-glucopyranosyl ester	*Terminalia Arjuna*		Amalraj and Gopi (2017), Modi et al. (2013)
12	Catechin	*Acacia Catechu*		Modi et al. (2013), Li et al. (2010), Li et al. (2011)
13	Kaempferol	*Acacia Catechu, Rosa damascene, Canthium coromandelicum, Oldenlandia diffusa*		Modi et al. (2013), Li et al. (2010), Li et al. (2011)
14	Procyanidin B-2	*Acacia Catechu*		Modi et al. (2013), Li et al. (2010), Li et al. (2011)
15	Leucocyanidin	*Saraca Indica*		Tandon and Yadav (2017), Sharma and Rangari (2016)
16	Isoforskolin	*Plectranthus Barbatus Andrews*		Haque et al. (2015)

Table 2 (continued)

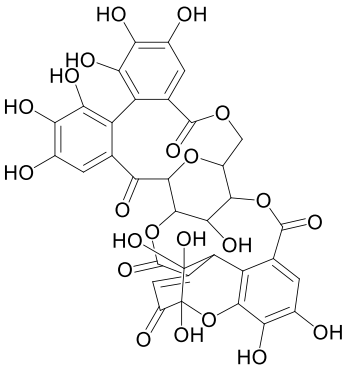
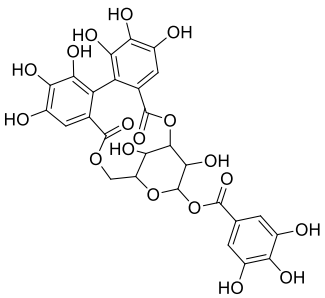
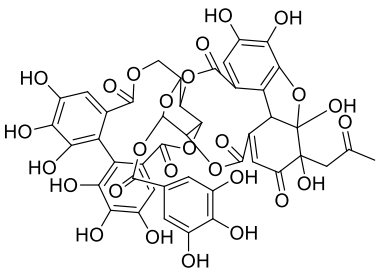
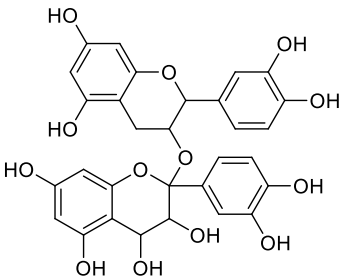
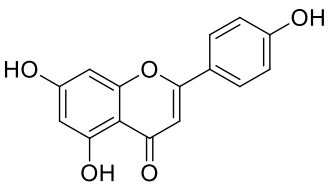
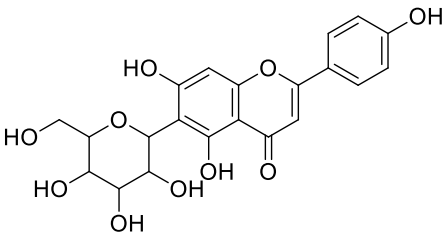
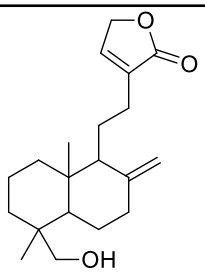
Sr.no	Phytoconstituents	Name of plant	Structure	References
17	Granatin A	*Punica granatum L*		Alasbahi and Melzig (2010b)
18	Corilagin	*Punica granatum L*		Alasbahi and Melzig (2010b)
19	Ellagitanin	*Punica granatum L*		Alasbahi and Melzig (2010b)
20	Procyanidin	*Adansonia Digitata L*		Braca et al. (2018)
21	Apigenin	*Adansonia Digitata L*		Braca et al. (2018)
22	Isovitexin	*Adansonia Digitata L*		Braca et al. (2018)

Table 2 (continued)

Sr.no	Phytoconstituents	Name of plant	Structure	References
23	Andrograpanin	*Andrographis Paniculata*		Niranjan Reddy et al. (2005)

Ailanthus altissima (Mill.) Swingle

Ailannthus altissima is commonly named as Ailanto or Tree of heaven. Ailanto is from Simaroubaceae family. It is used in several systems of medicine such as Folk medicine, Homeopathy and Traditional Chinese Medicine. It is cultivated in India and China. In India, this plant is distributed in Haryana, Himachal Pradesh, Kashmir, Assam, Punjab and Uttar Pradesh. Stem bark of this medicinal plant has cell fusion inhibitory activity. Methanol crude extract of this plant exhibited virus–cell fusion inhibitory activity with 74.9% inhibition (Chang and Woo 2003). Stem bark of Ailanto tree consists of Coumarin and Triterpenoid derivatives. Among these derivatives, Tetracyclic triterpenoids (Altissimanins A-E) has promising action against HIV cell fusion (Al-Snafi 2015; Hong et al. 2013).

Jatropha curcas L.

Jatropha curcas L. is a shrub known as Physic nut and Jangli Arandi. In India, it is cultivated in Andhra Pradesh, Assam, Bihar, Madhya Pradesh, Maharastra, Rajasthan, Tamil Nadu, and Uttar Pradesh. It is used in several systems of medicine such as Ayurveda, Folk medicine, Homoeopathy, Unani, Siddha, and Traditional Chinese medicine (Muanza et al. 1995; Matsuse et al. 1998). This shrub belongs to family Euphorbiaceae. 5,7-dimethoxycoumarin and 6,7-dimethoxycoumarin obtained from methanolic leaf extract showed moderate inhibition of HIV-1-induced cytopathic effect (IC_{50} = 9 µg/ml) with low cytotoxicity (Muanza et al. 1995; Matsuse et al. 1998).

Momordica charantia *L.*

Momordica charantia L. is also known as bitter gourd. It belongs to Cucurbitaceae family. It is used in several systems of medicine such as Ayurveda, Folk medicine, Homoeopathy, Unani, Siddha, Traditional Chinese medicine, and Sowa Rigpa. It is cultivated in Assam, Maharashtra, Gujarat, Tamil Nadu, Rajasthan, and Uttar Pradesh. Seed and fruit extracts of this plants are reported for the inhibition of syncytium formation. MAP 30 protein can be isolated from the fruits and seeds of the plant. MAP-30 protein showed 60% and 86% inhibition of syncytium formation at 1.67 nM and 1670 nM, respectively (Lee-Huang et al. 1991).

Anisomeles indica (L.) Kuntze

Anisomeles indica L. is mainly cultivated in Assam and Meghalaya. It is known as Kala Bhangra. It is used in several systems of medicine such as Folk medicine and Traditional Chinese medicine. Ovatodiolide a diterpenoid from *Anisomeles indica* showed potent anti-HIV activity with maximum cellular protection of 80–90%. Ovatodiolide inhibited cytopathic effects at an IC_{50} of 1.20 µg/ml (Bodiwala et al. 2009). List of phytoconstituents having HIV fusion inhibitory activity are mentioned in Table 4.

CCR5 and CXCR4 inhibitors:

The viral entry consists of complex sequence of events mediated by cellular membrane protein which interacts with viral glycoprotein gp120 and CD4 cellular receptor. Further interaction of such glycoprotein with any of the two co-receptors CC chemokine receptor 5 (CCR5) and CXC chemokine receptor 4 promote appropriate conformational modification during an early stage of the viral cycle (Dragic et al. 1996; Scarlatti et al. 1997). Recently, CCR5 and CXCR4 antagonist is suggested by the identification of viral stain tropism for clinical use. It inhibits the entry of virus (Kalinina et al. 2013). Some medicinal plant extracts are able to inhibit the HIV cell entry by inhibiting co-receptor CCR5 and CXCR4. Those medicinal plants is given below and in Table 5.

Avicennia marina var. rumphiana (Hallier f.) Bakh.

Avicennia marina is an Indian medicinal plant known as Gray mangrove. It is mainly distributed in Paleotropics. In India, it is cultivated in Kerala and Maharashtra. It is used in Folk medicine system. Iridoid glycoside namely

Table 3 Chemical structures of phytoconstituents having HIV integrase inhibitory activity

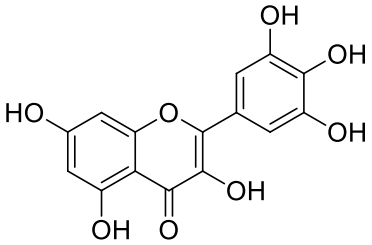
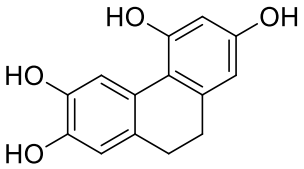
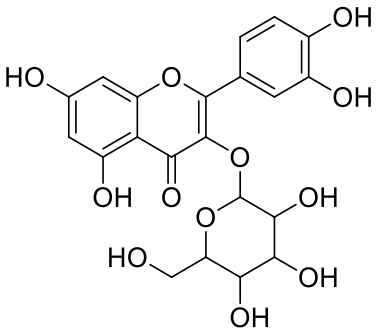
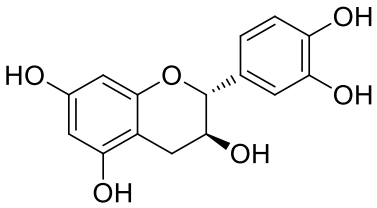
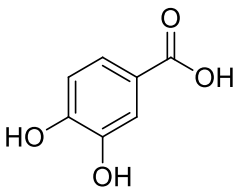
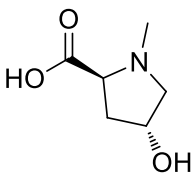
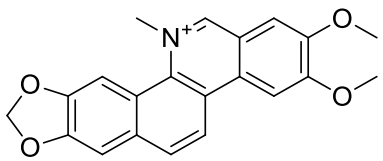
Sr.no	Phytoconstituents	Name of plant	Structure	References
1	Myricetin	*Dioscorea bulbifera L*		Chaniad et al. (2016)
2	2,4,6,7-tetrahydroxy-9,10-Dihydrophenanthrene	*Dioscorea bulbifera L*		Chaniad et al. (2016)
3	Quercetin-3-O-β-D-glucopyranoside	*Dioscorea bulbifera L*		Chaniad et al. (2016)
4	(+) Catechin	*Albizia procera*		Panthong et al. (2015)
5	Protocatechuic acid	*Albizia procera*		Panthong et al. (2015)
6	*N*-methyl-trans-4-hydroxy-L-proline	*Aglaia lawii*		Puripattanavong et al. (2016)
7	Nitidine	*Toddalia asiatica L*		Rashid et al. (1995)

Table 3 (continued)

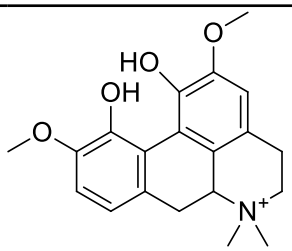
Sr.no	Phytoconstituents	Name of plant	Structure	References
8	Magnoflorine	*Toddalia asiatica L*		Rashid et al. (1995)

Table 4 Chemical structures of phytoconstituents having HIV fusion inhibitory activity

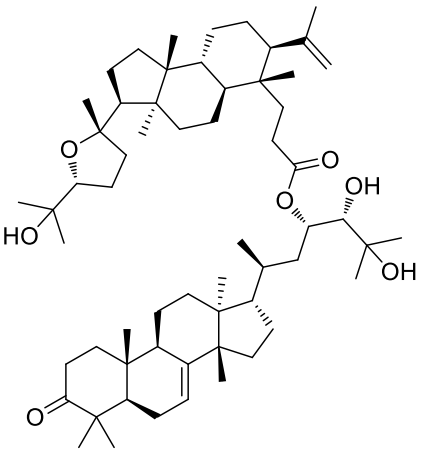
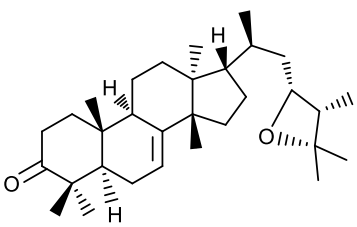
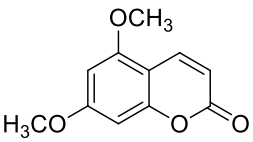
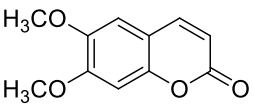
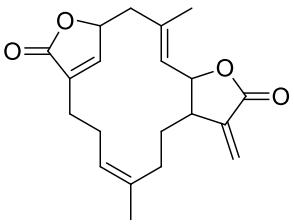
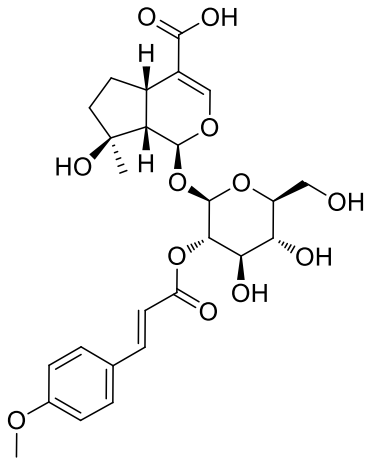
Sr.no	Phytoconstituents	Name of plant	Structure	References
1	Altissimanins E	*Ailannthus altissima*		Al-Snafi (2015), Hong et al. (2013)
2	Altissimanins A	*Ailannthus altissima*		Al-Snafi (2015), Hong et al. (2013)
3	5, 7- dimethoxycoumarin	*Jatropha curcas L*		Muanza et al. (1995), Matsuse et al. (1998)
4	6, 7,Dimethoxycoumarin	*Jatropha curcas L*		Muanza et al. (1995), Matsuse et al. (1998)
5	Ovatodiolide	*Anisomeles indica L*		Bodiwala et al. (2009)

Table 5 Chemical structures of phytoconstituents having CCR5 and CXCR4 inhibitory activity

Sr.no	Phytoconstituents	Name of plant	Structure	References
1	2′-O-(4-methoxycinnamoyl)mussaenosidic acid	*Avicennia marina*		Behbahani (2014), Feng et al. (2006)

2'-O-(4- methoxycinnamoyl)mussaenosidic acid isolated from *Avicennia marina* showed CCR5 and CXCR4 inhibitory activity. Methanolic seed extract of 2'-O-(4-methoxycinnamoyl)mussaenosidic acid is reported to inhibit the entry of retro virus through CCR5 and CXCR4 inhibition with 99% inhibition and EC_{50} of 0.1 µg/ml (Behbahani 2014; Feng et al. 2006).

Multi- target acting medicinal plants

A multi-target or hybrid drug can be defined as a chemical entity that combines the pharmacophores of two or more drugs with different mechanisms of action in a single molecule which is capable to interact simultaneously with two or more molecular targets (Castro and Camarasa 2018). Some of the medicinal plants with multi-targeted potencies for the treatment of HIV are reviewed below.

Arctium lappa L.

Arctium lappa L. belongs to Asteraceae family and it is known as Greater Burdock. It is used in several systems of medicine such as Folk medicine, Homoeopathy and Traditional Chinese medicine. *Arctium lappa L.* is generally used for skin diseases such as acne. It is cultivated from Middle East to India, China, Russia, Nepal, Afghanistan and Pakistan. Aerial part of Burdock has multi-targeted action against HIV. Burdock possesses anti-PR, anti-IN and cell fusion inhibition activity (Lam et al. 2000). Aqueous extract of *Arctium lappa L.* showed inhibitory activity against HIV-IN with 60% inhibition (Au et al. 2001). Results of cell fusion inhibitory activity indicated that 0% HIV antigen positive cells were present when cells were treated with the extract of this plant (Chang and Yeung 1988). Flavonoids and terpenes isolated from roots and leaves showed inhibitory activity against HIV-IN. Luteolin, Quercetin and Rutin are the flavonoids extracted from roots and leaves of *Arctium lappa L.* Various sesquiterpenes, sesquiterpene lactones and triterpenes can also be extracted from roots and leaves of this plant (Tobyn et al. 2000).

Senecio scandens

Senecio scandens belongs to Asteraceae family. It is easily cultivated in Indian subcontinent, South China, Philippines and Japan. It is used in several systems of medicine such as Folk medicine and Traditional Chinese medicine. It has multi-targeted action against HIV-PR and HIV-IN (Lam et al. 2000; Au et al. 2001). crude methanol and aqueous extract of the whole plant showed % HIV-PR inhibition with 83% and 81%, respectively (200 µg/ml concentration) (Lam et al. 2000). It elicited 60% inhibition of HIV-1 integrase activity at 50 µg/ml (Chang and Yeung 1988). β-sitosterol, pentacosanoic acid, 19α-H lupeone are also effective for HIV inhibitory activity (Wang et al. 2011).

Calophyllum inophyllum L.

Calophyllum inophyllum L. is known as Indian laurel or Alexandrian laurel. It is a tree from Clusiaceae family. General habitat of this tree is terrestrial. It is cultivated in Cambodia, China, India, Indonesia, Japan, Malaysia, Philippines, Sri Lanka, Thailand, Vietnam, Madagascar and Australasia. In India, it is obtained from Andaman and Nicobar Islands, Lakshadweep, Karnataka, Kerala, Odisha, Maharashtra and Tamil Nadu. It is used in Ayurvedic, Siddha and folk medicines, for treating eczema, insanity, syphilis and inflamed eyes. 'Tacamahaca' gum from wounded bark is used as

purgative and emetic. *Calophyllum inophyllum* has multi-targeting potential with anti-RT, anti-PR, and anti-IN activity (Narayan et al. 2011). Bark extract of this plant has very potent activity against HIV-IN and HIV-PR. Aqueous extract showed potent inhibitory action against HIV-IN with more than 90% inhibition (IC_{50} = 5.6 µg/ml). Ethanolic extract also showed more than 90% of HIV-IN inhibition with an IC_{50} of 9.8 µg/ml. HIV-PR inhibition was observed in aqueous extract and ethanolic extract with IC_{50} of 16.3 µg/ml and 63.8 µg/ml, respectively (Pawar et al. 2007). Inophyllum B (IC_{50} = 0.038 µM) and Inophyllum P (IC_{50} = 0.130 µM) are pyranocoumarins having inhibitory activity against HIV-RT with more than 90% inhibition (Laure et al. 2008; Patil et al. 1993).

Terminalia chebula Retz.

Terminalia chebula Retz. Belongs to Combretaceae family. It is known as black myrobalan. In Gujarat it is commonly known as Harade. It is used in several systems of medicine such as Ayurveda, Folk medicine, Homoeopathy, Unani, Siddha, Traditional Chinese medicine, and Sowa Rigpa. It is cultivated in Andhra Pradesh, Bihar, Gujarat, Himachal Pradesh, Karnataka, Kerala, Madhya Pradesh, Mahrastra, Odisha, Sikkim, Tamil Nadu, Tripura, Uttar Pradesh, and West Bengal. *Terminalia chebula* has multi-target inhibitory activity against HIV-RT, HIV-PR, and HIV-IN (Kumbhar et al. 2018). Fruit extract of this plant showed promising inhibitory action against HIV-RT, HIV-PR, and HIV-IN. Methanolic and aqueous fruit extract of the plant showed HIV-RT inhibitory activity with IC_{50} values of 2 µg/ml and 6 µg/ml, respectively (El-Mekkawy et al. 1995). Aqueous and methanolic, both the extracts of fruit showed 50% HIV-PR inhibition at a concentration of 0.2 mg/ml (Kusumoto et al. 1995). *T. chebula* has moderate HIV-IN inhibition with IC_{50} value of 10.3 µg/ml. Phytoconstituents of *T. Chebula* i.e., Gallic acid, 1,3,6-tri-O-galloyl-β-D-glucopyranose, 1,2,3,4,6-penta-O-galloyl-β-D-glucopyranose, and Chebulagic acid are promising agents for the treatment of HIV infection (Ahn et al. 2002).

Prunella vulgaris L.

Prunella vulgaris L. is knows as self-heal plant and belongs to the family Lamiaceae. It is used in several systems of medicine such as Folk medicine and Traditional Chinese medicine. It is cultivated in north temperate of Indian subcontinent, Europe, America, Australia and Sri Lanka. This plant has HIV-PR, HIV-IN and cell fusion inhibitory activity by interaction of viral gp120 with cell surface receptor, CD4 (Lam et al. 2000; Yao et al. 1992). Aqueous extract of whole plant showed activity against HIV-PR with 93% inhibition at a concentration of 200 mg/ml (Lam et al. 2000). Aqueous extract of this plant showed moderate inhibition of HIV-IN with an EC_{50} of 45 µg/ml (Au et al. 2001). *P. Vulgaris* extract also inhibited gp120-CD4 binding at K_i value of 2 µg/ml (Yao et al. 1992; Tabba et al. 1989). Triterpenes, flavonoids, and some of polyphenols with polysaccharide are promising phyoconstituents for the treatment of HIV infection (Gu et al. 2013; Oh et al. 2011). Triterpenoids are extracted from leaves and stem of *P. vulgaris*. Betulinic acid and 2α,3α-dihydroxyurs-12-en-28-oic acid are triterpenoids extracted from the leaves and stem of *P. vulgaris* have anti-HIV activity (Psotová et al. 2003; Kojima and Ogura 1986; Ryu et al. 1992).

Rosa damascena Mill.

Rosa damascena Mill. is known as Damask Rose belongs to Rosaceae family. It is cultivated in Maharashtra, Assam, and Meghalaya. It is used in various systems of medicine such as Ayurveda, Folk medicine, Homoeopathy, Unani and Siddha (Mahmood et al. 1996). Flavonoids have been shown to inhibit various Kaempferol and Quercetin reduced HIV infection by greater than 99% with EC_{50} of 0.8 µg/ml and 10 µg/ml, respectively (Mahmood et al. 1996; Nakane et al. 1991). Quercetin inhibited CD4/gp120 interaction, HIV-RT and HIV-PR activities. Kaempferol showed anti-HIV-PR activity with an IC_{50} of 2 µg/ml (Mahmood et al. 1996; Ono et al. 1990). One of the Kaempferol derivatives, Kaempferol 3-O-β-D glucopyranosides had little effect on protease enzyme but showed a significant reduction in gp120/CD4 interaction (Mahmood et al. 1996; Brinkworth et al. 1992).

Canthium coromandelicum (Burm.f.) Alston

Canthium coromandelicum is commonly known as Carray cheddie. This is the plant of Rubiaceae family. It is cultivated in Maharashtra, Tamil Nadu, Andhra Pradesh, Karnataka and Kerala. Leaf extract of *C. coromandelicum* showed HIV-1 reverse transcriptase inhibition and gp120 binding inhibition. Methanolic leaf extract of this plant reported to inhibit HIV-RT and gp120 binding with 78.67% and 72.52% inhibition (Chinnaiyan et al. 2013). Quercetin, Kaempferol and Astragalin are effective phytoconstituents of methanolic leaf extract with anti-HIV activity (Patro and Sasmal 2015).

Oldenlandia diffusa (Willd.) Roxb.

Oldenlandia diffusa belongs to family Rubiaceae. In Assam, it is known as Bon-jaluk. It is used in Folk medicine and Traditional Chinese medicine. It is cultivated in tropical and subtropical region of India. Aqueous extract of this plant showed more than 80% inhibition against HIV-PR at 250 µg/ml. This plant is reported to elicit moderate inhibition of HIV-IN enzyme. Chemical constituents of the whole plant

extract of *O. duffusa* are Quercetin, kaempferol, scopoletin, 2-hydroxy-3-methylanthraquinone, 2-hydroxy-l-methoxy-anthraquinone, α-linolenic acid, vanillic acid, p-hydroxy-phenylethanol and, β-sitosterol. Majorly, Quercetin and kaempferol showed anti-HIV activity among these phyo-constituents (Liang et al. 2008; Ganbold et al. 2010).

Eclipta prostrate (*L.*)

Eclipta prostrate L. is well known Indian medicinal plant of the family Asteraceae. It is also known as Bhringaraj. It is mainly cultivated in pantropical areas. In India, it is widely distributed in Uttrakhand. It is used in Ayurveda, Folk medicine, Siddha, and Traditional Chinese medicine. Whole plant parts are reported to exhibit anti-PR and anti-IN activity (Tewtrakul et al. 2007). 5-hydroxymethyl-(2,2′:5′,2″)- terthienyl tiglate, 5-hydroxymethyl-(2,2′:5′,2″)-terthienyl acetate and Ecliptal showed inhibition of HIV-PR with IC_{50} values 58 μM, 93 μM and 83 μM, respectively (Tewtrakul et al. 2007, 2006). Orobol and Wedelolactone showed HIV-PR inhibition with IC_{50} values of 8 μM and 4 μM, respectively (Tewtrakul et al. 2007; Han et al. 2015). List of phytoconstituents with multi-targeted activities are given in Table 6. Overall, a comprehensive list of all medicinal plants with their pharmacological activities are reported in Table 7.

Critical assessment and discussion

Nature has always provided the cure for the treatment of many complicated diseases including HIV. Over the past decades, promising developments have been made in the investigation of medicinal plants as anti-HIV agents. These agents belong to various structurally diverse scaffolds like coumarins, terpenes, alkaloids, flavonoids, tannins, etc. Most of these scaffolds serve as leads for the development of novel anti-HIV agents. This section describes the future of phytoconstituents reviewed here. For this purpose, a pharmacophore modeling was carried out using 14 diversified and representative phytoconstituents having anti-HIV activity on different enzymes and receptors (reverse transcriptase, protease, integrase, cell fusion, CCR5 and CXCR4).

Pharmacophore is a combination of chemical structural features and their biological activities. Pharmacophore mapping has proved successful role in ligand and structure based drug design for the development of potent bioactive molecules. Pharmacophore modeling is used to find common chemical structural features responsible for biological activity like hydrophobic region, hydrogen bond donor, and hydrogen bond acceptor from the diversified chemical structures. In present work, Pharmacophore modeling was performed using SYBYL X 1.2 software. All the phytoconstituents were drawn by SKETCH module of SYBYL X 1.2. The chemical structures of molecules used for pharmacophore generation is given in Table 8. Partial atomic charges were calculated by the Gasteiger Huckel method. A Tripos force field was used with a distance-dependent dielectric and the Powell conjugate gradient algorithm conjunction criterion of 0.01 kcal/mol Å during the process of energy minimization. A total number of 10 models were generated for each hypothesis using DISCOtech. The best model generated for each hypothesis by DISCOtech was again selected for refinement by Genetic algorithm similarity program (GASP). GASP is based on the genetic algorithm to characterize common features of different molecules from which hypothesis is generated. The objective of this step is to produce 3D query through proper alignment, to flatten out rings so that spatial query can be created for its use in substructure searching. By carrying out a GASP alignment, it is guaranteed that conformations which are used as input will look at least once in optimization. During this optimization, only stable and least energy conformer were retained and propagated to the next iteration of the genetic algorithm. All parameters were kept as default other than population size (125), mutation weight (96), fitness increment (0.02) and number of alignment (10).

After following the above mentioned procedure, A 3D Pharmacophore query was generated consisting of 4 features including donor site, donor atom, acceptor atom and hydrophobic region as depicted in Fig. 2a. For better understating of inter feature geometric distance responsible for interaction with biological target, a 2D pharmacophore model is also shown in Fig. 2b. (Bhatt et al. 2014b; Patel and Bhatt 2021).

These 4 features generated from pharmacophore can be used to design and discover potent and bioactive anti-HIV molecules. Based on the generated pharmacophore, structural requirements for anti-HIV activity is highlighted in Fig. 3.

Presence of hydrophobic ring like phenyl and fusion of phenyl ring with heterocyclic rings (for example chromane ring) are essential for the anti-HIV activity. These ring systems are beneficial for multi target activities on different HIV enzymes. Substitutions on the phenyl ring with H-bond donor atoms like oxygen and nitrogen are critical for inhibition of HIV Protease, Integrase and cell fusion. Moreover, phenyl ring can be substituted with H-bond donor groups like –OH, $-NH_2$ and –COOH for specific inhibition of Protease enzyme. Substitutions on heterocyclic ring with H-bond acceptor atoms and acceptor functional groups like –C = O and $–OCH_3$ impart Reverse transcriptase, Integrase, CCR5 and CXCR4 inhibitory activities. Overall, the present study may facilitate the development of future leads from bioactive natural products for the treatment of HIV.

Table 6 Chemical structures of phytoconstituents having multi-targeted inhibitory activity

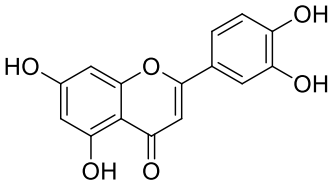
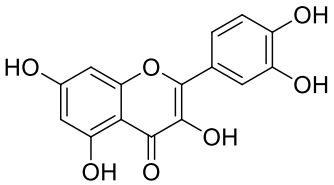
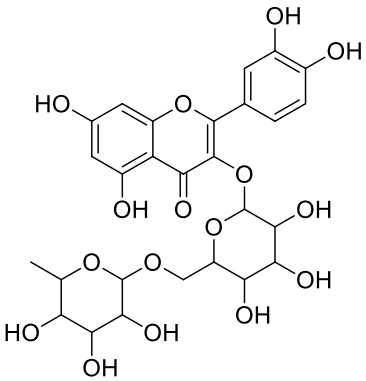
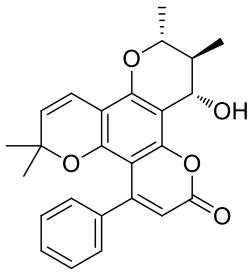
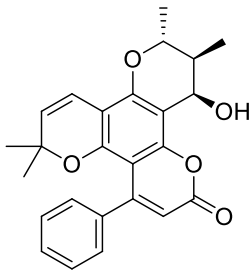
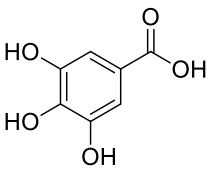
Sr.no	Phytoconstituents	Name of plant	Structure	References
1	Luteolin	*Arctium lappa L*		Tobyn et al. (2000)
2	Quercetin	*Arctium lappa L, Rosa damascena*		Tobyn et al. (2000)
3	Rutin	*Arctium lappa L*		Tobyn et al. (2000)
4	Inophyllum B	*Calophyllum inophyllum L*		Laure et al. (2008), Patil et al. (1993)
5	Inophyllum P	*Calophyllum inophyllum L*		Laure et al. (2008), Patil et al. (1993)
6	Gallic Acid	*Terminalia chebula Retz*		Ahn et al. (2002)

Table 6 (continued)

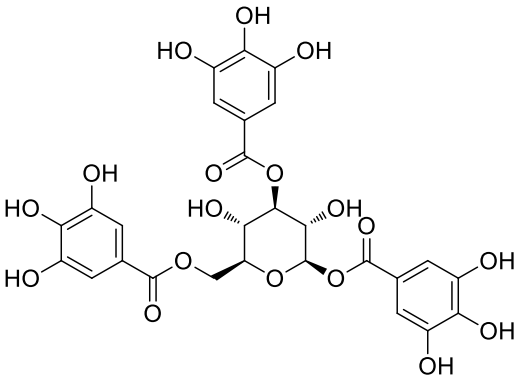
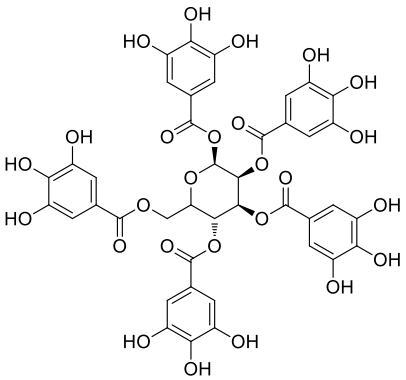
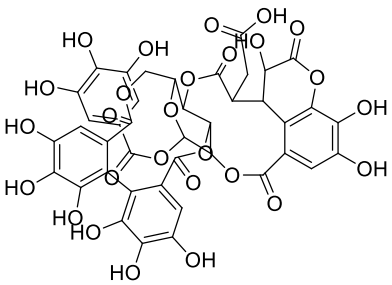
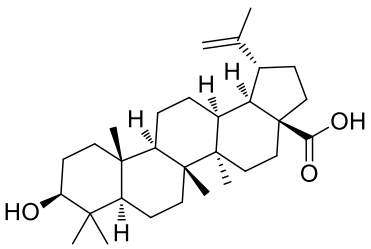
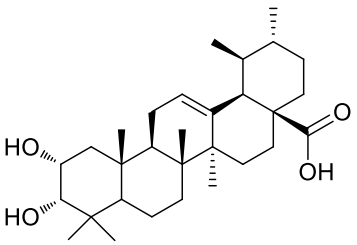
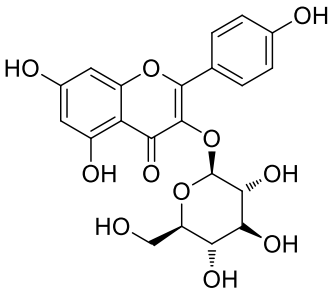
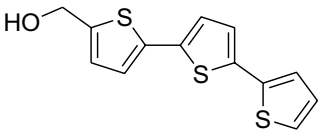
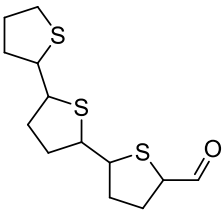
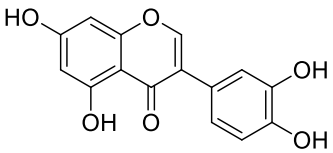
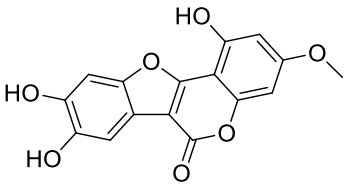
Sr.no	Phytoconstituents	Name of plant	Structure	References
7	1,3,6-tri-O-galloyl-β-D-glucopyranose	*Terminalia chebula Retz*		Ahn et al. (2002)
8	1,2,3,4,6-penta-O-galloyl-β-D- glucopyranose	*Terminalia chebula Retz*		Ahn et al. (2002)
9	Chebulagic acid	*Terminalia chebula Retz*		Ahn et al. (2002)
10	Betulinic acid	Prunella vulgaris L		Psotová et al. (2003), Kojima and Ogura (1986), Ryu et al. (1992)
11	2α, 3α-dihydroxyurs-12-en-28-oic acid	Prunella vulgaris L		Psotová et al. (2003), Kojima and Ogura (1986), Ryu et al. (1992)

Table 6 (continued)

Sr.no	Phytoconstituents	Name of plant	Structure	References
12	Astragalin	*Canthium coromandelicum*		Patro and Sasmal (2015)
13	5-hydroxym-ethyl-(2,2′:5′,2″)- ter-thienyl tiglate	*Eclipta prostrate*		Tewtrakul et al. (2007), Tewtrakul et al. (2006)
14	Ecliptal	*Eclipta prostrate*		Tewtrakul et al. (2007), Tewtrakul et al. (2006)
15	Orobol	*Eclipta prostrate*		Tewtrakul et al. (2007), Han et al. (2015)
16	Wedelolactone	*Eclipta prostrate*		Tewtrakul et al. (2007), Han et al. (2015)

Conclusion

Acquired Immune Deficiency Syndrome (AIDS) is one of the leading causes of death worldwide. Current treatment available for HIV/AIDS have certain limitations like severe side effects and drug resistance so, there is an urgent need for safe, effective and functional treatment for HIV. Tropical countries are endowed with a rich source of medicinal plants with encouraging therapeutic activities. This review provides an insight about the medicinal plants having anti-HIV properties. Medicinal plants are classified as Reverse transcriptase (RT) inhibitors, Protease (PR) inhibitors, Integrase (IN) inhibitors, cell fusion inhibitors, CC chemokine receptor 5 (CCR5) and CXC chemokine receptor 4 (CXCR4) inhibitors and muti-target inhibitors. Further, phytoconstituents present in an individual plant with their anti-HIV potencies are elaborated. Pharmacophore modeling was performed using these phytoconstituents for generation of potent leads for future development of anti-HIV drugs. This review may become helpful in identifying new treatment strategy using natural source for the treatment of HIV.

Table 7 A comprehensive list of pharmacological activities of tropical medicinal plants

Medicinal plants	Activity	References
Justicia Gendurussa	**Anti-RT** activity of Crude water extract: 90% IR at 200 µg/ml	Maartens et al. (2014), Woradulayapinij et al. (2005)
Acorus calamus L	**Anti-RT** activity of crude hexane extract: IC_{50} = 33.96 µg/ml	Silprasit et al. (2011)
Allium Sativum L	**Anti-RT** activity of crude hexane extract: > 80% IR	Silprasit et al. (2011)
Hemidesmus Indicus	**Anti-RT** Activity **Lupeol:** RDDP enzyme inhibition IC_{50} = > 100 µM; RNase H function inhibition IC_{50} = 11.6 µM **Lupeol acetate:** RDDP enzyme inhibition IC_{50} = 100 µM; RNase H function inhibition IC_{50} = 63 µM	Esposito et al. (2017)
Canna Indica L	**Anti-RT** activity of crude water extract: 92% IR at 200 µg/ml	Woradulayapinij et al. (2005)
Anogeissus Acuminata	**Anti-RT** activity: Anolignan A and Anolignan B combined IC_{50} = 30–50 µg/ml	Rimando et al. (1994)
Swertia Franchetiana	**Anti-RT** activity **Swertifrancheside:** ED_{50} = 30.9 µg/ml **Swertipunicoside:** ED_{50} = 3.0 µg/ml	Pengsuparp et al. (1995), Wang et al. (1994)
Vitex Trifolia L	**Anti-RT** activity of crude water extract: 98.06% inhibition at 200 µg/ml	Woradulayapinij et al. (2005)
Artocarpus Heterophyllus Lam	**Anti-RT** activity of crude seed extract: > 80% IR at 0.225 mg/ml	Silprasit et al. (2011)
Plumbago Indica L	**Anti-RT** activity of crude root extract: > 80% IR at 0.225 mg/ml	Silprasit et al. (2011)
Areca Catechu L	**Anti-PR** activity of crude water extract: 71.5% inhibition; crude methanol extract: 84.1% inhibition **Arecatannin A1:** IC_{50} = 0.5 mM **Arecatannin B1:** IC_{50} = 0.5 mM	Kusumoto et al. (1995)
Terminalia Arjuna	**Anti-PR** activity of crude bark water extract: 80% inhibition; crude methanol extract: 83% inhibition	Kusumoto et al. (1995), Xu et al. (1996)
Acacia Catechu	**Anti-PR** activity of crude n-butanol extract: IC_{50} = 12.9 µg/ml at 50 µg/ml **Epicatechin:** IC_{50} = 0.60 µg/ml	Modi et al. (2013)
Acacia Nilotica	**Anti-PR** activity of crude pods, water extract: 48% inhibition; crude methanol extract: 57% inhibition	Hussein et al. (1999)
Saraca Indica	**Anti-PR** activity of crude water extract: 84% inhibition at 0.2 mg/ml	Kusumoto et al. (1995)
Plectranthus Barbatus Andrews	**Anti-PR** activity of crude ethanol extract IC_{50} = 62.0 µg/ml	Kapewangolo et al. (2013)
Punica granatum L	**Anti-PR** activity of crude water extract: 88% inhibition at 250 µg/ml	Kusumoto et al. (1995), Xu et al. (1996)
Adansonia Digitata L	**Anti-PR** activity of crude ethanol leaf extract: 75% inhibition at 50 µg/ml; pulp extract: 74% inhibition at 50 µg/ml	Sharma and Rangari (2016)
Andrographis Paniculata	**Anti-PR** activity **Andrographolide:** EC_{50} = 49.0 µg/mL **14-deoxy-11,12-didehydroandrographolide:** EC_{50} = 56.8 µg/mL	Niranjan Reddy et al. (2005)

Table 7 (continued)

Medicinal plants	Activity	References
Dioscorea bulbifera L	**Anti-IN** activity **Myricetin:** IC_{50} = 3.15 µM **2,4,6,7-tetrahydroxy-9,10-dihydrophenanthrene:** IC_{50} = 14.20 µM **Quercetin-3-O-β-D-glucopyranoside:** IC_{50} = 19.39 µM **Quercetin-3-O-β-D-galactopyranoside**: IC_{50} = 21.80 µM	Chaniad et al. (2016)
Albizia procera (Roxb.) Benth	**Anti-IN** activity of crude bark water extract IC_{50} = 5.9 µg/ml	Bunluepuech and Tewtrakul* (2011), Panthong et al. (2015)
Aglaia lawii (Wight) C.J. Saldanha	**Anti-IN** activity ***N*-methyl-trans-4-hydroxy-L-proline**: IC_{50} = 11.8 µg/ml	Puripattanavong et al. (2016)
Toddalia asiatica (L.) Lam	**Anti-IN** activity **Nitidine: % inhibition range =** 1-10 µg/ml	Rashid et al. (1995)
Ailanthus altissima (Mill.) Swingle	**Cell fusion inhibitory activity** of methanol crude extract = 74.9% inhibition	Chang and Woo (2003)
Jatropha curcas L	**Cell fusion inhibitory activity** 5,7-dimethoxycoumarin and 6,7-dimethoxycoumarin methanol leaf extract = IC_{50} = 9 µg/ml	Muanza et al. (1995), Matsuse et al. (1998)
Momordica charantia L	**Inhibition of syncytium formation** MAP-30 (isolated from fruit) = 60% inhibition at 1.67 nM MAP-30 (isolated from seeds) = 86% inhibition at 1670 nM	Lee-Huang et al. (1991)
Anisomeles indica (L.) Kuntze	**Cytopathic effect** Ovatodiolide: IC_{50} = 1.20 µg/ml	Bodiwala et al. (2009)
Avicennia marina var. rumphiana (Hallier f.) Bakh	**CCR5 and CXCR4 inhibition** **2'-O-(4-methoxycinnamoyl)mussaenosidic acid:** CCR5 = 99% inhibition and CXCR4 = EC_{50} of 0.1 µg/ml	Behbahani (2014), Feng et al. (2006)
Arctium lappa L	**Multi-target activity** **Anti-IN** activity: 60% inhibition, cell-fusion inhibition	Au et al. (2001)
Senecio scandens	**Multi-target activity** **Anti-PR** activity of crude methanol extract of the whole plant % inhibition = 83%, water extract = 81%, at 200 µg/ml **Anti-IN** activity of crude extract: % inhibition = 60% at 50 µg/ml	Lam et al. (2000), Chang and Yeung (1988)
Calophyllum inophyllum L	**Multi-target activity** **Anti-IN** activity of crude water extract: IC_{50} = 5.6 µg/ml **Anti-IN** activity of crude ethanol extract: IC_{50} = 9.8 µg/ml **Anti-PR** activity of crude water extract: IC_{50} = 16.3 µg/ml **Anti-PR** activity of crude ethanol extract: IC_{50} = 63.8 µg/ml **Anti-RT** activity: **Inophyllum B:** IC_{50} = 0.038 µM **Inophyllum P**: IC_{50} = 0.130 µM	Pawar et al. (2007), Laure et al. (2008), Patil et al. (1993)
Terminalia chebula Retz	**Multi-target activity** **Anti-RT** activity of crude methanol fruit extract: IC_{50} = 2 µg/ml **Anti-RT** activity of crude water fruit extract: IC_{50} = 6 µg/ml **Anti-IN** activity of plant: IC_{50} = 10.3 µg/ml	El-Mekkawy et al. (1995), Ahn et al. (2002)

Table 7 (continued)

Medicinal plants	Activity	References
Prunella vulgaris L	**Multi-target activity** **Anti-PR** activity of crude water extract (whole plant): % inhibition = 93% at 200 mg/ml **Anti-IN** activity of crude water extract (whole plant): EC_{50} = 45 µg/ml **Cell-fusion inhibition**: K_i = 2 µg/ml	Lam et al. (2000), Au et al. (2001) Yao et al. (1992), Tabba et al. (1989)
Rosa damascena Mill	**Multi-target activity** **Kaempferol:** EC_{50} = 0.8 µg/ml (HIV inhibition); **Anti-PR** activity: IC_{50} = 2 µg/ml **Quercetin:** EC_{50} = 10 µg/ml (CD4/gp120 interaction, HIV-RT and HIV-PR activities)	Mahmood et al. (1996), Nakane et al. (1991), Ono et al. (1990)
Canthium coromandelicum (Burm.f.) Alston	**Multi-target activity** **Anti-RT** activity of Methanol leaf extract: 78.67% inhibition **Gp120 binding:** 72.52% inhibition	Chinnaiyan et al. (2013)
Oldenlandia diffusa (Willd.) Roxb	**Multi-target activity** **Anti-PR** activity of crude water extract: % inhibition = 80% at 250 µg/ml	Liang et al. (2008), Ganbold et al. (2010)
Eclipta prostrate (*L.*)	**Multi-target activity** **Anti-PR activity** 5-hydroxymethyl-(2,2′:5′,2″)-terthienyl tiglate: IC_{50} = 58 µM 5-hydroxymethyl-(2,2′:5′,2″)-terthienyl acetate: IC_{50} = 93 µM Ecliptal: IC_{50} = 83 µM Orobol: IC_{50} = 8 µM Wedelolactone: IC_{50} = 4 µM	Tewtrakul et al. (2007), Tewtrakul et al. (2006), Han et al. (2015)

Table 8 Chemical structures of phytoconstituents used for pharmacophore model generation

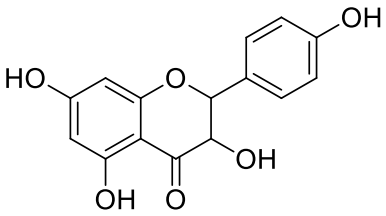
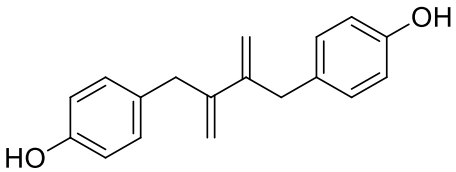
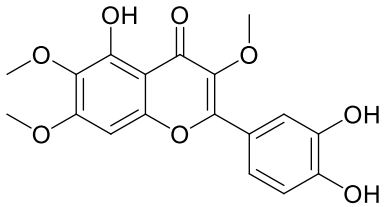
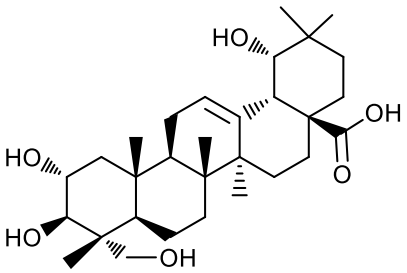
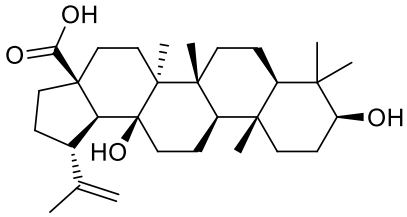
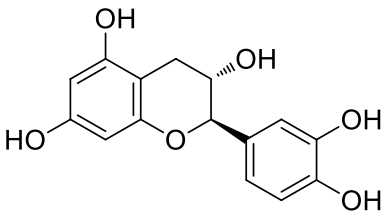
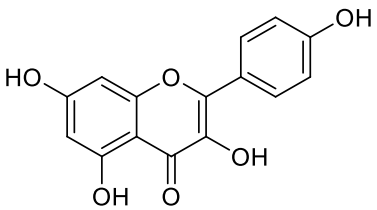
Name of Phytoconstituents		Target enzyme/receptor
Aromadendrin		HIV Reverse transcriptase
Anolignan B		HIV Reverse transcriptase
3,6,7-trimethylquercetagetin		HIV Reverse transcriptase
Arjungenin		HIV Protease
Terminic Acid		HIV Protease
Catechin		HIV Protease
Kaempferol		HIV Protease

Table 8 (continued)

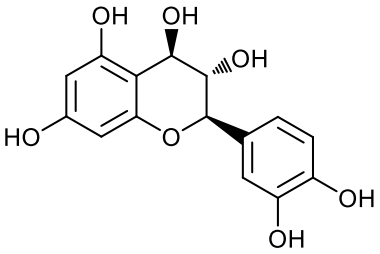
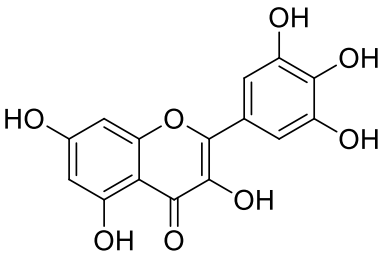
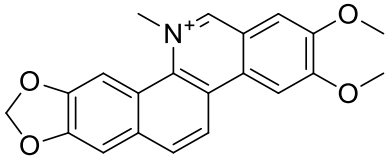
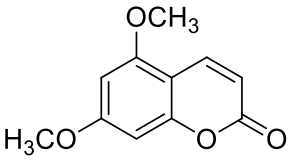
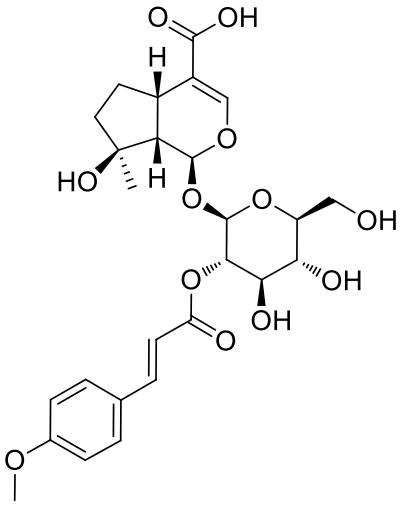
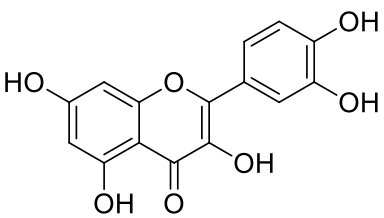
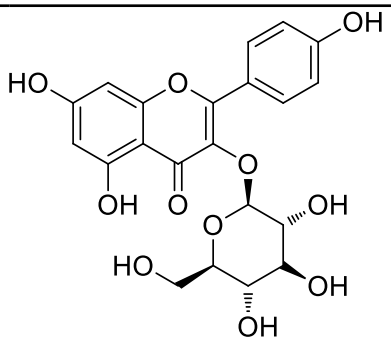
Name of Phytoconstituents		Target enzyme/receptor
Leucocyanidin		HIV Protease
Myricetin		HIV integrase
Nitidine		HIV integrase
5, 7- dimethoxycoumarin		HIV fusion inhibitor
2′-O-(4-methoxycinnamoyl)mussaenosidic acid		CCR5 and CXCR4 inhibitor
Quercetin		Multi-targeted inhibitor

Table 8 (continued)

Name of Phytoconstituents		Target enzyme/receptor
Astragalin		Multi-targeted inhibitor

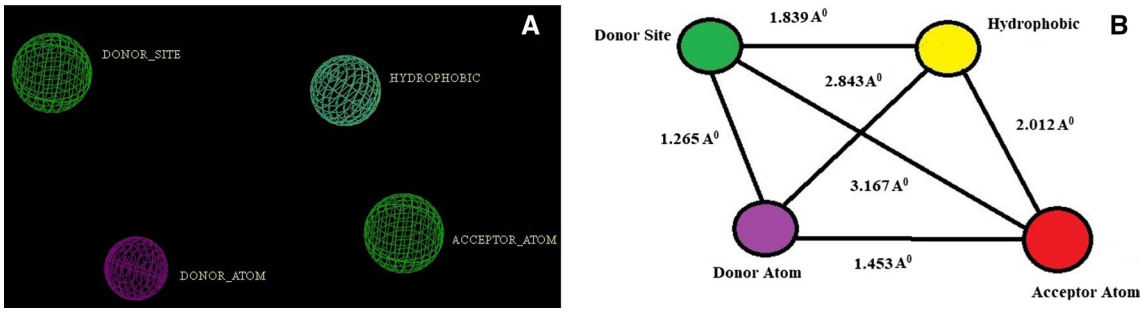


Fig. 2 Pharmacophore generated from anti-HIV Phytoconstituents **a** 3D representation of Pharmacophore **b** 2D representation of Pharmacophore

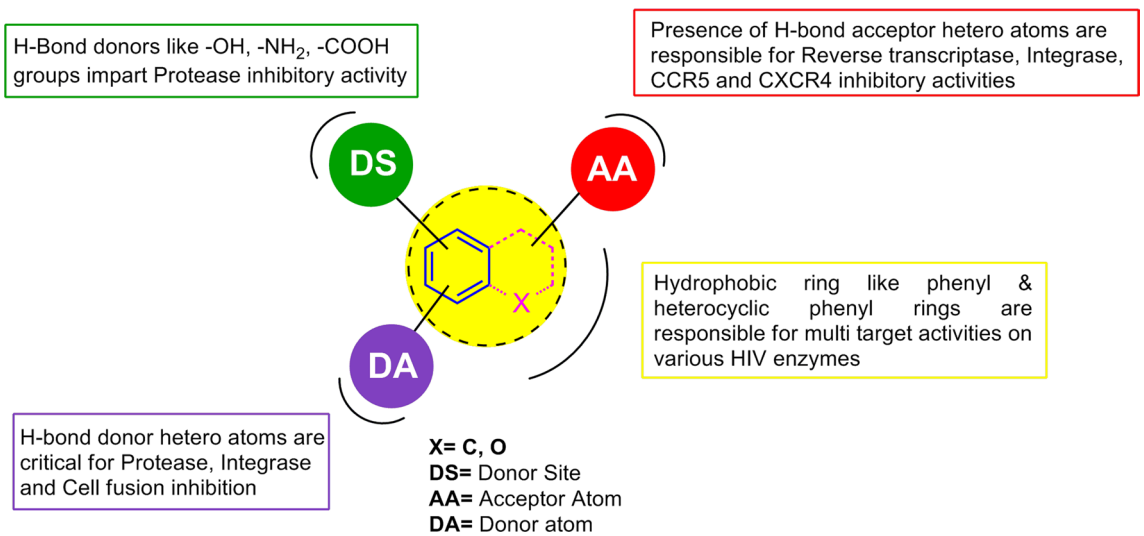


Fig. 3 Outcome of Pharmacophore modeling

Acknowledgements The authors PKP and HGB are thankful to Nirma University, Ahmedabad, India for providing necessary facilities to carry out the work, which is a part of Doctor of Philosophy (Ph.D.) research work of Mr. Paresh Patel, to be submitted to Nirma University, Ahmedabad, India. The authors DVP, SRS and PKP are also thankful to L. J. Institute of Pharmacy, L J University, Ahmedabad, India for providing necessary support.

Author contribution DVP, SRS and PKP carried out literature search, compilation of data and preparation of manuscript. HGB & PKP supervised the work and revised the manuscript.

Funding sources No funding source has been utilized in this work.

Declarations

Ethical statement This article does not contain any studies involving animals performed by any of the authors. This article does not contain any studies involving human participants performed by any of the authors.

Conflict of interest Dharmraj V. Pathak has no conflict of interest. Sneha R. Sagar has no conflict of interest. Hardik G. Bhatt has no conflict of interest. Paresh K. Patel has no conflict of interest.

References

Ahn M-J, Kim CY, Lee JS et al (2002) Inhibition of HIV-1 integrase by galloyl glucoses from Terminalia chebula and flavonol glycoside gallates from Euphorbia pekinensis. Planta Med 68(5):457–459

Al-Snafi AE (2015) The pharmacological importance of Ailanthus altissima-A review. Int J Pharm Rev Res 5(2):121–129

Alasbahi RH, Melzig MF (2010a) Plectranthus barbatus: a review of phytochemistry, ethnobotanical uses and pharmacology–part 2. Planta Med 76(8):753–765

Alasbahi RH, Melzig MF (2010b) Plectranthus barbatus: a review of phytochemistry, ethnobotanical uses and pharmacology–part 1. Planta Med 76(7):653–661

Amalraj A, Gopi S (2017) Medicinal properties of Terminalia arjuna (Roxb.) Wight & Arn.: a review. J Tradit Complement Med (1): 65–78

Anjaneyulu ASR, Prasad AVR (1983) Structure of terminic acid, a dihydroxytriterpene carboxylic acid from Terminalia arjuna. Phytochemistry 22(4):993–998

Au TK, Lam TL, Ng TB et al (2001) A comparison of HIV-1 integrase inhibition by aqueous and methanol extracts of Chinese medicinal herbs. Life Sci 68(14):1687–1694

Bartlett JA, Shao JF (2009) Successes, challenges, and limitations of current antiretroviral therapy in low-income and middle-income countries. Lancet Infect Dis 9(10):637–649

Basavaraj KH, Navya MA, Rashmi R (2010) Quality of life in HIV/AIDS. Indian J Sex Transm Dis AIDS 31(2):75

Behbahani M (2014) Evaluation of anti-HIV-1 activity of a new iridoid glycoside isolated from Avicenna marina, in vitro. Int Immunopharmacol 23(1):262–266

Bhatt H, Patel P, Pannecouque C (2014a) Discovery of HIV-1 integrase inhibitors: pharmacophore mapping, virtual screening, molecular docking, synthesis, and biological evaluation. Chem Biol Drug Des 83(2):154–166

Bodiwala HS, Sabde S, Mitra D, et al (2009) Anti-HIV Diterpenes from Coleus forskohlii. Nat Prod Commun 4(9): 1934578X0900400902

Boireau S, Maiuri P, Basyuk E et al (2007) The transcriptional cycle of HIV-1 in real-time and live cells. J Cell Biol 179(2):291–304

Braca A, Sinisgalli C, De Leo M, et al (2018) Phytochemical profile, antioxidant and antidiabetic activities of Adansonia digitata L.(Baobab) from Mali, as a source of health-promoting compounds. Molecules 23(12): 3104

Brinkworth RI, Stoermer MJ, Fairlie DP (1992) Flavones are inhibitors of HIV-1 proteinase. Biochem Biophys Res Commun 188(2):631–637

Bunluepuech K, Tewtrakul* S (2011) Anti-HIV-1 integrase activity of Thai medicinal plants in longevity preparations. Sonklanakarin J Sci Technol 33(6): 693

Cagigi A, Mowafi F, Phuong Dang LV et al (2008) Altered expression of the receptor-ligand pair CXCR5/CXCL13 in B cells during chronic HIV-1 infection. Blood 112(12):4401–4410

de Castro S, Camarasa M-J (2018) Polypharmacology in HIV inhibition: can a drug with simultaneous action against two relevant targets be an alternative to combination therapy? Eur J Med Chem 150:206–227

Chang Y, Woo E (2003) Korean medicinal plants inhibiting to Human Immunodeficiency Virus type 1 (HIV-1) fusion. Phyther Res an Int J Devoted to Pharmacol Toxicol Eval Nat Prod Deriv 17(4):426–429

Chang RS, Yeung HW (1988) Inhibition of growth of human immunodeficiency virus in vitro by crude extracts of Chinese medicinal herbs. Antiviral Res 9(3):163–175

Chaniad P, Wattanapiromsakul C, Pianwanit S, Tewtrakul S (2016) Anti-HIV-1 integrase compounds from Dioscorea bulbifera and molecular docking study. Pharm Biol 54(6):1077–1085

Chinnaiyan SK, Subramanian MR, Kumar SV, et al (2013) Antimicrobial and anti-HIV activity of extracts of Canthium coromandelicum (Burm. f.) Alston leaves. J Pharm Res 7(7): 588–594

Cihlar T, Ray AS (2010) Nucleoside and nucleotide HIV reverse transcriptase inhibitors: 25 years after zidovudine. Antiviral Res 85(1):39–58

Degroote S, Vogelaers D, Vandijck DM et al (2014) What determines health-related quality of life among people living with HIV: an updated review of the literature. Arch Public Heal 72:1–10

Dinda B, Das SK, Hajra AK, et al (2019) Chemical constituents of Plumbago indica roots and reactions of plumbagin: Part II

Dragic T, Litwin V, Allaway GP et al (1996) HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5. Nature 381(6584):667–673

El-Mekkawy S, Meselhy MR, Kusumoto IT, et al (1995) Inhibitory effects of egyptian folk medicines oh human immunodeficiency virus (HIV) reverse transcriptase. Chem Pharm Bull 43(4):641–648

Esposito F, Mandrone M, Del Vecchio C, et al (2017) Multi-target activity of Hemidesmus indicus decoction against innovative HIV-1 drug targets and characterization of Lupeol mode of action. Pathog Dis 75(6): ftx065

Feng Y, Li X, Duan X, Wang B (2006) Iridoid glucosides and flavones from the aerial parts of Avicennia marina. Chem Biodivers 3(7):799–806

Ganbold M, Barker J, Ma R et al (2010) Cytotoxicity and bioavailability studies on a decoction of Oldenlandia diffusa and its fractions separated by HPLC. J Ethnopharmacol 131(2):396–403

Ghosh AK, Osswald HL, Prato G (2016) Recent progress in the development of HIV-1 protease inhibitors for the treatment of HIV/AIDS. J Med Chem 59(11):5172–5208

Group W-H (2003) Preliminary development of the World Health Organsiation's Quality of Life HIV instrument (WHOQOL-HIV): analysis of the pilot version. Soc Sci Med 57(7): 1259–1275

Gu X, Li Y, Mu J, Zhang Y (2013) Chemical constituents of Prunella vulgaris. J Environ Sci 25:S161–S163

Hamarsheh O (2020) HIV/AIDS in palestine: a growing concern. Int J Infect Dis 90:18–20

Han L, Liu E, Kojo A, et al (2015) Qualitative and quantitative analysis of Eclipta prostrata L. by LC/MS. Sci World J

Haque N, Sofi G, Ali W et al (2015) A comprehensive review of phytochemical and pharmacological profile of Anar (Punica granatum Linn): a heaven's fruit. J Ayurvedic Herb Med 1(1):22–26
Hegde S, Hegde HV, Jalalpure SS et al (2017) Resolving identification issues of Saraca asoca from its adulterant and commercial samples using phytochemical markers. Pharmacogn Mag 13:S266
Hoenigl M, Green N, Camacho M et al (2016) Signs or symptoms of acute HIV infection in a cohort undergoing community-based screening. Emerg Infect Dis 22(3):532
Honda T, Murae T, Tsuyuki T, et al (1976) Arjungenin, arjunglucoside I, and arjunglucoside II. A new triterpene and new triterpene glucosides from Terminalia arjuna. Bull Chem Soc Jpn 49(11): 3213–3218
Hong Z-L, Xiong J, Wu S-B et al (2013) Tetracyclic triterpenoids and terpenylated coumarins from the bark of Ailanthus altissima ("Tree of Heaven"). Phytochemistry 86:159–167
https://indiabiodiversity.org/. Accessed on 21th April 2020
https://eol.org/. Accessed on 21th April 2020
https://aidsinfo.unaids.org/. Accessed on 12th March 2020.
Hussein G, Miyashiro H, Nakamura N et al (1999) Inhibitory effects of Sudanese plant extracts on HIV-1 replication and HIV-1 protease. Phyther Res an Int J Devoted to Pharmacol Toxicol Eval Nat Prod Deriv 13(1):31–36
Kalinina OV, Pfeifer N, Lengauer T (2013) Modelling binding between CCR5 and CXCR4 receptors and their ligands suggests the surface electrostatic potential of the co-receptor to be a key player in the HIV-1 tropism. Retrovirology 10(1):1–11
Kapewangolo P, Hussein AA, Meyer D (2013) Inhibition of HIV-1 enzymes, antioxidant and anti-inflammatory activities of Plectranthus barbatus. J Ethnopharmacol 149(1):184–190
Kirchhoff F (2013) HIV life cycle: overview. Encyclopedia of AIDS, 1–9
Kojima H, Ogura H (1986) Triterpenoids from Prunella vulgaris. Phytochemistry 25(3):729–733
Kumbhar ST, Patil SP, Une HD (2018) Phytochemical analysis of Canna indica L. roots and rhizomes extract. Biochem Biophys Rep 16: 50–55
Kusumoto IT, Nakabayashi T, Kida H et al (1995) Screening of various plant extracts used in ayurvedic medicine for inhibitory effects on human immunodeficiency virus type 1 (HIV-1) protease. Phyther Res 9(3):180–184
Lam TL, Lam ML, Au TK et al (2000) A comparison of human immunodeficiency virus type-1 protease inhibition activities by the aqueous and methanol extracts of Chinese medicinal herbs. Life Sci 67(23):2889–2896
Laure F, Raharivelomanana P, Butaud J-F et al (2008) Screening of anti-HIV-1 inophyllums by HPLC–DAD of Calophyllum inophyllum leaf extracts from French Polynesia Islands. Anal Chim Acta 624(1):147–153
Lee-Huang S, Kung H, Huang PL et al (1991) A new class of anti-HIV agents: GAP31, DAPs 30 and 32. FEBS Lett 291(1):139–144
Levy JA, Mackewicz CE, Barker E (1996) Controlling HIV pathogenesis: the role of the noncytotoxic anti-HIV response of CD8+ T cells. Immunol Today 17(5):217–224
Li X-C, Liu C, Yang L-X, Chen R-Y (2011) Phenolic compounds from the aqueous extract of Acacia catechu. J Asian Nat Prod Res 13(9):826–830
Li X, Wang H, Liu C, Chen R (2010) Chemical constituents of Acacia catechu. Zhongguo Zhong yao za zhi= Zhongguo zhongyao zazhi= China journal of Chinese materia medica 35(11): 1425–1427
Liang Z, He M, Fong W, et al (2008) A comparable, chemical and pharmacological analysis of the traditional Chinese medicinal herbs Oldenlandia diffusa and O. corymbosa and a new valuation of their biological potential. Phytomedicine 15(4): 259–267
Maartens G, Celum C, Lewin SR (2014) HIV infection: epidemiology, pathogenesis, treatment, and prevention. Lancet 384(9939):258–271
Mahmood N, Piacente S, Pizza C et al (1996) The anti-HIV activity and mechanisms of action of pure compounds isolated fromRosa damascena. Biochem Biophys Res Commun 229(1):73–79
Martins N, Petropoulos S, Ferreira ICFR (2016) Chemical composition and bioactive compounds of garlic (Allium sativum L.) as affected by pre-and post-harvest conditions: a review. Food Chem 211: 41–50
Matsuse IT, Lim YA, Hattori M, et al (1998) A search for anti-viral properties in Panamanian medicinal plants.: the effects on HIV and its essential enzymes. J Ethnopharmacol 64(1): 15–22
Modi M, Dezzutti CS, Kulshreshtha S et al (2013) Extracts from Acacia catechu suppress HIV-1 replication by inhibiting the activities of the viral protease and Tat. Virol J 10(1):1–17
Moore RC, Fazeli PL, Jeste DV et al (2014) Successful cognitive aging and health-related quality of life in younger and older adults infected with HIV. AIDS Behav 18(6):1186–1197
Muanza DN, Euler KL, Williams L, Newman DJ (1995) Screening for antitumor and anti-HIV activities of nine medicinal plants from Zaire. Int J Pharmacogn 33(2):98–106
Nakane H, Arisawa M, Fujita A et al (1991) Inhibition of HIV-reverse transcriptase activity by some phloroglucinol derivatives. FEBS Lett 286(1–2):83–85
Narayan C, Rai RV, Tewtrakul S (2011) A screening strategy for selection of anti-HIV-1 integrase and anti-HIV-1 protease inhibitors from extracts of Indian medicinal plants. Int J Phytomedicine 3(3):312
Niranjan Reddy VL, Malla Reddy S, Ravikanth V et al (2005) A new bis-andrographolide ether from Andrographis paniculata nees and evaluation of anti-HIV activity. Nat Prod Res 19(3):223–230
Oh C, Price J, Brindley MA et al (2011) Inhibition of HIV-1 infection by aqueous extracts of Prunella vulgaris L. Virol J 8(1):1–10
Ono K, Nakane H, Fukushima M et al (1990) Differential inhibitory effects of various flavonoids on the activities of reverse transcriptase and cellular DNA and RNA polymerases. Eur J Biochem 190(3):469–476
Panthong P, Bunluepuech K, Boonnak N et al (2015) Anti-HIV-1 integrase activity and molecular docking of compounds from Albizia procera bark. Pharm Biol 53(12):1861–1866
Patel PK, Bhatt HG (2020) Improved 3D-QSAR prediction by multiple-conformational alignments and molecular docking studies to design and discover HIV-I protease inhibitors. Curr HIV Res 19(2):154–171
Patel PK, Bhatt HG (2021) Improved 3D-QSAR prediction by multiple conformational alignments and molecular docking studies to design and discover HIV-I protease inhibitors. Curr HIV Res 19(2):154–171
Patel SB, Patel BD, Pannecouque C, Bhatt HG (2016) Design, synthesis and anti-HIV activity of novel quinoxaline derivatives. Eur J Med Chem 117:230–240
Patil AD, Freyer AJ, Eggleston DS et al (1993) The inophyllums, novel inhibitors of HIV-1 reverse transcriptase isolated from the Malaysian tree. Calophyllum Inophyllum Linn J Med Chem 36(26):4131–4138
Patro SK, Sasmal D (2015) Invitro Antioxidant study and search for a novel bioactive compound from leave fractions of canthium coromandelicum (Burm. F.) Alston. Int J Pharm Sci Res 6(9): 3841
Pawar KD, Joshi SP, Bhide SR, Thengane SR (2007) Pattern of anti-HIV dipyranocoumarin expression in callus cultures of Calophyllum inophyllum Linn. J Biotechnol 130(4):346–353

Pelay-Gimeno M, Glas A, Koch O, Grossmann TN (2015) Structure-based design of inhibitors of protein–protein interactions: mimicking peptide binding epitopes. Angew Chemie Int Ed 54(31):8896–8927

Pengsuparp T, Cai L, Constant H et al (1995) Mechanistic evaluation of new plant-derived compounds that inhibit HIV-1 reverse transcriptase. J Nat Prod 58(7):1024–1031

Pironti A, Pfeifer N, Kaiser R et al (2014) Improved therapy-success prediction with GSS estimated from clinical HIV-1 sequences. J Int AIDS Soc 17:19743

Psotová J, Kolář M, Soušek J et al (2003) Biological activities of Prunella vulgaris extract. Phyther Res an Int J Devoted Pharmacol Toxicol Eval Nat Prod Deriv 17(9):1082–1087

Puripattanavong J, Tungcharoen P, Chaniad P et al (2016) Anti-HIV-1 integrase effect of compounds from Aglaia andamanica leaves and molecular docking study with acute toxicity test in mice. Pharm Biol 54(4):654–659

Ranasinghe RA, Maduwanthi SD, Marapana RA (2019) Nutritional and health benefits of jackfruit (Artocarpus heterophyllus Lam.): a review. Int J Food Sci 4327183

Rashid MA, Gustafson KR, Kashman Y et al (1995) Anti-HIV alkaloids from Toddalia asiatica. Nat Prod Lett 6(2):153–156

Rimando AM, Pezzuto JM, Farnsworth NR et al (1994) New lignans from Anogeissus acuminata with HIV-1 reverse transcriptase inhibitory activity. J Nat Prod 57(7):896–904

Rodriguez-Penney AT, Iudicello JE, Riggs PK et al (2013) Co-morbidities in persons infected with HIV: increased burden with older age and negative effects on health-related quality of life. AIDS Patient Care STDS 27:5–16

Row LR, Murty PS, Rao GSRS, et al (1970) Chemical examination of Terminalia species. XII. Isolation & structure determination of arjunic acid, a new trihydroxytriterpene carboxylic acid from Terminalia arjuna bark. Indian J Chem 8: 716–721

Ryu SY, Lee C-K, Lee CO et al (1992) Antiviral triterpenes from Prunella vulgaris. Arch Pharm Res 15(3):242–245

Sabde S, Bodiwala HS, Karmase A et al (2011) Anti-HIV activity of Indian medicinal plants. J Nat Med 65(3–4):662–669

Salehi B, Kumar NVA, Şener B et al (2018) Medicinal plants used in the treatment of human immunodeficiency virus. Int J Mol Sci 19(5):1459

Scarlatti G, Tresoldi E, Björndal Å et al (1997) In vivo evolution of HIV-1 co-receptor usage and sensitivity to chemokine-mediated suppression. Nat Med 3(11):1259–1265

Senapati SK, Das GK, Aparajita S, Rout GR (2012) Assessment of genetic variability in the Asoka tree of India. Biodiversity 13(1):16–23

Sharma A, Rangari V (2016) HIV-1 reverse transcriptase and protease assay of methanolic extracts of Adansonia digitata L. Int J Pharm Pharm Sci 8:124–127

Shirolkar A, Gahlaut A, Chhillar AK, Dabur R (2013) Quantitative analysis of catechins in Saraca asoca and correlation with antimicrobial activity. J Pharm Anal 3(6):421–428

Silprasit K, Seetaha S, Pongsanarakul P et al (2011) Anti-HIV-1 reverse transcriptase activities of hexane extracts from some Asian medicinal plants. J Med Plants Res 5(19):4899–4906

Simon V, Ho DD, Karim QA (2006) HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. Lancet 368(9534):489–504

Singh B, Singh VP, Pandey VB, Rücker G (1995) A new triterpene glycoside from Terminalia arjuna. Planta Med 61(6):576–577

Singh DV, Verma RK, Gupta MM, Kumar S (2002a) Quantitative determination of oleane derivatives in Terminalia arjuna by high performance thin layer chromatography. Phytochem Anal an Int J Plant Chem Biochem Tech 13(4):207–210

Singh DV, Verma RK, Singh SC, Gupta MM (2002b) RP-LC determination of oleane derivatives in Terminalia arjuna. J Pharm Biomed Anal 28(3–4):447–452

Srivastava GN, Bagchi GD, Srivastava AK (1988) Pharmacognosy of Ashoka stem bark and its adulterants. Int J Crude Drug Res 26(2):65–72

Suchitra M, Cheriyan BV (2018) Vitex trifolia: an ethnobotanical and pharmacological review. Asian J Pharm Clin Res 11(4):12–14

Tabba HD, Chang RS, Smith KM (1989) Isolation, purification, and partial characterization of prunellin, an anti-HIV component from aqueous extracts of Prunella vulgaris. Antiviral Res 11(5–6):263–273

Tandon N, Yadav SS (2017) Contributions of Indian Council of Medical Research (ICMR) in the area of Medicinal plants/Traditional medicine. J Ethnopharmacol 197:39–45

Tewtrakul S, Subhadhirasakul S, Cheenpracha S, Karalai C (2007) HIV-1 protease and HIV-1 integrase inhibitory substances from Eclipta prostrata. Phyther Res an Int J Devoted Pharmacol Toxicol Eval Nat Prod Deriv 21(11):1092–1095

Tewtrakul S, Subhadhirasakul S, Kummee S (2006) Anti-HIV-1 integrase activity of medicinal plants used as self medication by AIDS patients. Songklanakarin J Sci Technol 28(4):785–790

Tobyn G, Denham A, Whitelegg M (2016) The Western herbal tradition: 2000 years of medicinal plant knowledge. Singing Dragon

Vernekar SKV, Liu Z, Nagy E et al (2015) Design, synthesis, biochemical, and antiviral evaluations of C6 benzyl and C6 biarylmethyl substituted 2-hydroxylisoquinoline-1, 3-diones: dual inhibition against HIV reverse transcriptase-associated RNase H and polymerase with antiviral activities. J Med Chem 58(2):651–664

Wang W, Ali Z, Shen Y et al (2010) Ursane triterpenoids from the bark of Terminalia arjuna. Fitoterapia 81(6):480–484

Wang J-N, Hou C-Y, Liu Y-L et al (1994) Swertifrancheside, an HIV-reverse transcriptase inhibitor and the first flavone-xanthone dimer, from Swertia franchetiana. J Nat Prod 57(2):211–217

Wang CF, Li JP, Zhang YB, Zhang ZZ (2011) Chemical constituents from the roots of Senecio scandens. Chem Nat Compd 47(2):243–245

Wilen CB, Tilton JC, Doms RW (2012) HIV: cell binding and entry. Cold Spring Harb Perspect Med 2(8):a006866

Woradulayapinij W, Soonthornchareonnon N, Wiwat C (2005) In vitro HIV type 1 reverse transcriptase inhibitory activities of Thai medicinal plants and Canna indica L. rhizomes. J Ethnopharmacol 101(1–3): 84–89

Xu H, Wan M, Loh B et al (1996) Screening of traditional medicines for their inhibitory activity against HIV-1 protease. Phyther Res 10:207–210

Xu Z, Zhao S-J, Lv Z-S et al (2019) Fluoroquinolone-isatin hybrids and their biological activities. Eur J Med Chem 162:396–406

Yadav M, Sehrawat A, Kumar D, Bhidhasra A (2017) Therapeutic plants and phytoconstituents as natural anti-HIV agents: a review. Inven Rapid Planta Act 2017:1–5

Yao X-J, Wainberg MA, Parniak MA (1992) Mechanism of inhibition of HIV-1 infection in vitro by purified extract of Prunella vulgaris. Virology 187(1):56–62

Zaitseva E, Zaitsev E, Melikov K et al (2017) Fusion stage of HIV-1 entry depends on virus-induced cell surface exposure of phosphatidylserine. Cell Host Microbe 22(1):99–110

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.