Revista Brasileira de Farmacognosia 29 (2019) 504–528

Brazilian Journal of Pharmacognosy
REVISTA BRASILEIRA DE FARMACOGNOSIA
www.elsevier.com/locate/bjp

Review

Chemical diversity and activity profiles of HIV-1 reverse transcriptase inhibitors from plants

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ARTICLE INFO

Article history:
Received 30 August 2018
Accepted 1 October 2018
Available online 2 June 2019

Keywords:
HIV-1
Reverse transcriptase
Inhibitors
Phytochemicals
Inhibitory profiles

ABSTRACT

Current challenges to antiretroviral therapy have opened new vistas in the search for novel drugs from natural products. This review focusses on plants as sources of inhibitors for human immunodeficiency virus type 1 (HIV-1) reverse transcriptase. Based on a systematic search of the literature, anti-HIV-1 reverse transcriptase activity was recorded for 132 plant species in 100 genera and 51 families. Seven families comprise 52.6% of plant species with anti-reverse transcriptase activity: Lamiaceae (13.7%), Fabaceae (10.7%), Euphorbiaceae (9.9%), Clusiaceae (6.1%), Asteraceae (4.6%), Combretaceae (4.6%), and Moraceae (3.0%). The repertoire of anti-reverse transcriptase active compounds includes (−)-catechin, 1,8-cineole, 3,4-di-*O*-caffeoylquinic acid, 5,7-dimethoxy-6-methylflavone, apigenin, baicalein, betulinic acid, caffeic acid, *cis*-3-hexene-1-ol, eugenol, euscaphic acid, gallic acid, hoslunddiol, limonene, naringenin, oleanolic acid, *p*-cymene, pomolic acid, quinic acid, rosmarinic acid, stigmasterol, thymol, ursolic acid, α-bergamotene, α-pinene, and γ-terpinene. Among the IC_{50} values are 0.10 μg/ml (*Uvaria angolensis*), 3 μg/ml (Hemidesmus indicus), 2.3 μg/ml (*Adansonia digitata*), 6.24 μg/ml (*Caesalpinia coriaria*), 7.2 μg/ml (*Terminalia sericea*), 17.4 μg/ml (*Hypoxis hemerocallidea*), and 79 μg/ml (*Moringa oleifera*). The chemical diversity and activity profiles of HIV-1 reverse transcriptase inhibitors from plants reveal two recurring motifs: the structure of several active anti-reverse transcriptase compounds mimics nucleoside analogues, and numerous anti-reverse transcriptase phytochemicals have pleiotropic effects and heterogenous pharmacological benefits during infection and disease. To accelerate drug discovery and development, this review recommends the urgent need to tap into the rich vein of indigenous knowledge of putative anti-HIV/AIDS medicinal plants (reverse pharmacology), determine pan-assay interference compounds, analyze structure–activity relationships, and conduct more clinical trials.

Introduction

Globally, about 36.9 million people were living with human immunodeficiency virus (HIV) in 2017 (UNAIDS, 2018). HIV infection compromises the body's immune system leading to acquired immunodeficiency syndrome (AIDS). HIV type 1 (HIV-1) reverse transcriptase (RT) possesses both RNA-dependent DNA polymerase (RDDP) and ribonuclease H (RNase H) activities that work in tandem to convert viral genomic single-stranded RNA to double-stranded DNA that is then integrated into the DNA of the infected host cell (Figiel et al., 2018). RT-associated RDDP and RNase H functions are essential for HIV-1 genome replication. Among the HIV-1 RT inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTI) constitute a prominent class of drugs which for almost 20 years has served as the cornerstone of combination antiretroviral therapy (cART) (Poongavanam et al., 2018; Sluis-Cremer, 2018). NNRTI are small molecules that bind to HIV-1 RT at a site distinct from the DNA polymerase active site of the enzyme and block HIV-1 reverse transcription *via* an allosteric mechanism of action (Sluis-Cremer, 2018). The conformation of RT for RNA hydrolysis is distinctly different from that for DNA synthesis and reveals a structural cavity which serves as a target for RT inhibition (Tian et al., 2018).

Nevirapine was the first NNRTI approved in 1996 by the United States of America (USA) Food and Drug Administration (FDA) for the treatment of HIV-1 infection, followed by delavirdine in 1997, efavirenz in 1998, etravirine in 2008, and rilpivirine in 2011 (Sluis-Cremer, 2018). About 21.7 million people were accessing cART in 2017 (UNAIDS, 2018). However, the efficiency of NNRTI is undermined by adverse events, poor drug–drug interactions, and drug-resistant variants of HIV-1 RT (Chinsembu, 2016; Peltenburg et al., 2018). Even in naïve patients who are not yet on cART, HIV-1 mutant variants with residues that confer resistance to RT inhibitors form small pockets of the viral population (Ding et al., 2018).

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https://doi.org/10.1016/j.bjp.2018.10.006

In African countries such as Kenya, Nigeria, South Africa, Uganda, Zambia, and Zimbabwe, the overall prevalence of HIV resistance is 5.6%; this includes 3.3% associated with NNRTI (Hamers et al., 2011). People living with HIV who develop drug-resistant HIV have few other treatment options except regimens based on ritonavir-boosted protease inhibitors (Sörstedt et al., 2018). Still, protease and integrase inhibitors result in inferior virological outcomes, more HIV resistance, and are less likely recommended by current treatment protocols (Orkin et al., 2018). Severe liver toxicity affects 8–23% of HIV-infected patients receiving indinavir and tenofovir (Lemoine and Ingiliz, 2012), and cART is associated with nephrotoxicity (Hamzah and Post, 2009). Development of HIV resistance and toxicity subtract from the efficacy of and adherence to cART.

Against this backdrop, it is important to discover alternative HIV-1 RT inhibitors from plants. Therefore, the current review details the chemical diversity and biological activity profiles of HIV-1 RT inhibitors from plants. Detailed knowledge of plant chemical compounds that inhibit RDDP and RNase H functions is significant in the search for novel antiretroviral drugs. In the face of current challenges to cART, this review may inspire a new future where plants are the frontier for more efficacious HIV-1 RT inhibitors, in addition to creating a strong bioprospecting pipeline for innovative bioentrepreneurs to advance the invention of new HIV-1 RT drugs from plants.

Methodology

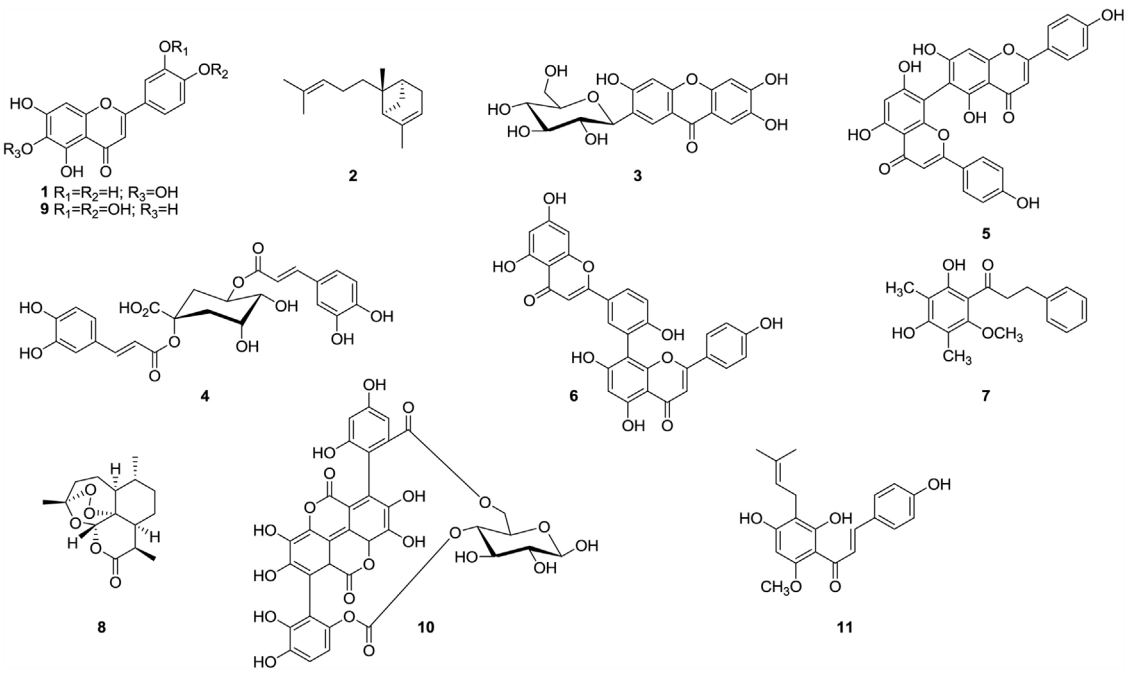
To prevent author bias, this review was carried out using a comprehensive and systematic data mining approach. To obtain pertinent literature, the key words "HIV reverse transcriptase inhibitors" and "plants" were concomitantly searched in Google Scholar, Elsevier's pay-to-view service ScienceDirect, Scopus, Scielo, and PubMed Central, the United States of America National Library of Medicine's digital archive of biomedical and life sciences journal literature. Literature sources included peer reviewed journal articles, conference/seminar proceedings, PhD theses, refereed books and abstracts. Further, only plants with known anti-RT activities were included in the study. Mushrooms, algae, plants with unknown anti-RT activities, and plants with anti-HIV-1 integrase or anti-HIV-1 protease activities were excluded.

Families and species of plants, phytochemical compounds and anti-RT profiles mainly half maximal inhibitory concentration (IC_{50}) were recorded. Where IC_{50} values were absent, the following anti-RT parameters were documeted: effective concentration (EC_{50}), inhibitory dose (ID_{50}), median effective dose (ED_{50}), and percentage inhibition of RT. Many of the RT assays used a non-radioactive HIV-RT colorimetric ELISA kit from Roche, Germany. International Plant Names Index (http://www.ipni.org) and The Plant List (http://www.theplantlist.org) were used to verify names of plant families and species. PubChem Structure Search was used to corroborate chemical structures of phytochemical compounds. The results of the review are presented and discussed in the following sections.

Plants, phytochemical compounds and anti-HIV RT activities

Box 1 shows the plant species, genera and families with their phytochemical diversity and HIV-1 RT inhibitory profiles. Overall, HIV-1 RT inhibitory activity was found in 132 plant species distributed across 100 genera and 51 families. Most of the plant species were principally distributed among the following families (Fig. 1): Lamiaceae (13.7%), Fabaceae (10.7%), Euphorbiaceae (9.9%), Clusiaceae (6.1%), Asteraceae (4.6%), Combretaceae (4.6%), and Moraceae (3.0%). These seven families consist of 52.6% of plant species with anti-HIV-1 RT activity. Plant species in the family Lamiaceae potently inhibit HIV-1 replication (Bedoya et al., 2001; Reichling et al., 2008; Geuenich et al., 2008). Other studies have found that plant species in the family Fabaceae and Euphorbiaceae inhibit HIV-1 RT (Chang et al., 1995; Ng et al., 1997; Matsuse et al., 1998; Matthée et al., 1999). Chinsembu and Hedimbi (2010) found that 65 plant species mostly from the Fabaceae family had anti-HIV activity and Prinsloo et al. (2018) documented 56 anti-HIV plant species from Southern Africa. Other studies have also documented anti-HIV-1 RT from plants (Li et al., 2018a,b,c; Ornano et al., 2018; Palacios, 2018).

In the leading plant families, the following phytochemicals were predominant: (−)-catechin, 1,8-cineole, 3,4-di-*O*-caffeoylquinic acid, 5,7-dimethoxy-6-methylflavone, apigenin, apigenin-7-*O*-glucoronide, apigenin-7-*O*-glucoside, apigenin-7-*O*-rutinoside, baicalein (**1**), betulinic acid, caffeic acid, *cis*-3-hexene-1-ol, eugenol, euscaphic acid, gallic acid, hoslunddiol, limonene, naringenin, oleanolic acid, *p*-cymene, pomolic acid, quinic acid, rosmarinic acid, stigmasterol, thymol, thymoquinone, ursolic acid, α-bergamotene (**2**), α-pinene, β-pinene and γ-terpinene. Other notable phytochemical compounds from plant extracts with anti-RT activities were: 1,3,6,7-tetrahydroxyxanthone or mangiferin (**3**), 1,5-dicaffeoylquinic acid (**4**), 1,8-cineole, 2-(3,3-dimethylallyl)-1,3,7-trihydroxyxanthone, 2-methylene-5-(1-methylethyl), 3-*O*-acetyl-aleuritolic acid, 3-*O*-acetyl-erythrodiol, 6-hydroxyl kaempferol 3-*O*-arabinoglucoside, 6β-angeloyloxy-3β,8α-dihydroxyeremophil-7(11)-en-12,8β-olide, 6β-angeloyloxy-3β,8β-dihydroxyeremophil-7(11)-en-12,8α-olide, agathisflavone (**5**), amentoflavone (**6**), angoletin (**7**), anisic acid, apetalic acid, artemisinin (**8**), bergenin, calanolides B and C, caloinophyllin A, camphene, camphor, centratherin and its derivative isocentratherin, chlorogenic acid, corydine, dicaffeoyl acids, digitoxigenin-3-*O*-glucoside, ellagic acid, ferulic acid, friedelane-3-one-28-al, friedelin, fumaric acid, garcinuntabiphenyls A–C, garcinuntins A–C, garciosones A–D, garcisaterpenes A and C, hinokiflavone, hinokiflavone, inophyllum B, isobavachalcone, lupenediol, lupenoic acid, luteolin (**9**), michellamine B, morelloflavone, nobiletin, norisoboldine, pentamethylquercetin, *p*-hydroxybenzoic acid, proteins such as acaconin and acafusin, punicalin (**10**), protostanes, quercelagetin 3,7-dimethylether, quercetin, repandusinic acid, rhusflavanone, robustaflavone, robustaflavone,



shikimic acid, stigmasta-4,22-dien-3-one, vanillic acid, vismiaphenone D, volkensiflavone, α-thujone, and xanthohumol (**11**).

In terms of anti-RT profiles, the IC_{50} values included 0.10 μg/ml for *Uvaria angolensis*, 3 μg/ml for *Hemidesmus indicus*, 2.3 μg/ml for *Adansonia digitata*, 6.24 μg/ml for *Caesalpinia coriaria*, 7.2 μg/ml for *Terminalia sericea*, 17.4 μg/ml for *Hypoxis hemerocallidea*, and 79 μg/ml for *Moringa oleifera*. EC_{50} values included 4.2 μg/ml for extracts of *Andrographis paniculata*, 1 μM for michellamine B isolated from a fraction of *Ancistrocladus korupensis*, 20.9 μg/ml for artemisinin (**8**) isolated from *Artemisia annua*, 1–2 μg/ml for water extracts of *Petasites japonicus*, 0.50 μg/ml for xanthohumol (**11**) isolated from *Humulus lupulus*, and 11 μg/ml for vismiaphenone D isolated from *Vismia cayennensis*. ED_{50} values included 7.6 μg/ml for a *p*-cymene and γ-terpinene-rich fraction of *Thymus serpyllum*, 1.6 μg/ml for rosmarinic acid isolated from *Melissa officinalis*, 7.1 μg/ml for polyphenolics isolated from *Perilla frutescens*, and 7.6 μg/ml for essential oils from *Lavandula dentata*.

Knowledge of plant species, genera and families in addition to their phytochemical diversity and HIV-1 RT inhibitory profiles may help demystify the use of plant remedies for managing HIV infection. This is important because in at least fourteen African countries, 80% or more of people who were estimated to be eligible for cART under the 2013 WHO guidelines were not on cART as of December 2012 (Chinsembu, 2016). Nine out of every ten people have an unmet need for cART in sub-Saharan African countries such as Angola, Cameroon, Central African Republic, Chad, Cote d'Ivoire, Democratic Republic of the Congo, Ethiopia, Ghana, Kenya, Lesotho, Malawi, Mozambique, Nigeria, South Africa, South Sudan, Togo, Uganda, Tanzania, Zambia and Zimbabwe. In 2007, only less than 10% of all HIV-infected children in need of cART in sub-Saharan Africa were actually receiving therapy (Eley and Nuttall, 2007). In these countries (especially for children), plant products with known anti-RT efficacy can become the new window of dispensary in the management of HIV infection and AIDS.

A remarkable diversity of phytochemical structures including proteins, terpenoids, coumarins, xanthones, alkaloids, flavonoids, polyphenols, and polysaccharides are capable of rendering HIV-1 RT less active (Ng et al., 1997). Plants may serve as sources of new active leads that may be developed further into anti-HIV drug candidates. In a 24 week study, a Chinese preparation of fourteen plants increased plasma CD4 counts and reduced HIV viral loads (Deng et al., 2014). In Zambia, the Sondashi Formula (SF2000), tested in human HIV patients, reduced viral loads and increased CD4 counts (Chinsembu, 2009; 2015). Phytochemicals such as calanolides (coumarins), ursolic and betulinic acids (triterpenes), and baicalin (flavonoid) are promising candidates for anti-HIV RT agents (Salehi et al., 2018).

By 2006, more than fifty chemical compounds with varying levels of anti-HIV activity had been isolated from plants (Chinsembu, 2016). Although the use of plants is a strong pipeline for the discovery of HIV-1 RT inhibitors, the anti-HIV-1 RT evidence presented in this paper provides a fresh quest to reconsider the mainstreaming of plant medications in the treatment of HIV/AIDS. In resource-poor settings, anti-RT plants can be used as herbal drugs to manage HIV/AIDS. Medicinal plants are not a replacement for cART (Chinsembu, 2009), but they do increase the options available to AIDS patients, especially those faced by side-effects due to antiretroviral drugs, HIV resistance and treatment failure (WHO, 1989; Homsy et al., 2004). Anti-HIV-1 RT compounds from plants may provide leads to novel and more efficacious drugs to lessen the global burden of HIV/AIDS. Conservation of anti-HIV plants is important to ensure sustainability and avoid medicinal plant extinction. As research into new anti-HIV agents focuses on novel structures and (or) new action mechanisms (Yu et al., 2003), the chemical diversity of plant compounds in this review can be utilized as herbal antiretroviral drugs or used in the search for novel compounds with anti-RT activities.

Recurring motifs in chemical diversity and activity profiles of HIV-1 RT inhibitors from plants

Structure dictates function

The first recurring motif illustrated in this review relates to the structure of the plant compounds with anti-HIV-1 RT inhibitory activity. Much like the first ART drug azidothymidine (AZT) which was approved for AIDS treatment in 1987, several active anti-RT plant compounds mimic nucleoside analogues in one structural shape or form. They appear to be close homologues that share structural and functional similarities with NNRTI. This is true for chemical compounds such as (−)-catechin, 1,5-dicaffeoylquinic acid (**4**), agathisflavone (**5**), amentoflavone (**6**), angoletin (**7**), apigenin, artemisinin (**8**), baicalein (**1**), betulinic acid, ellagic acid,

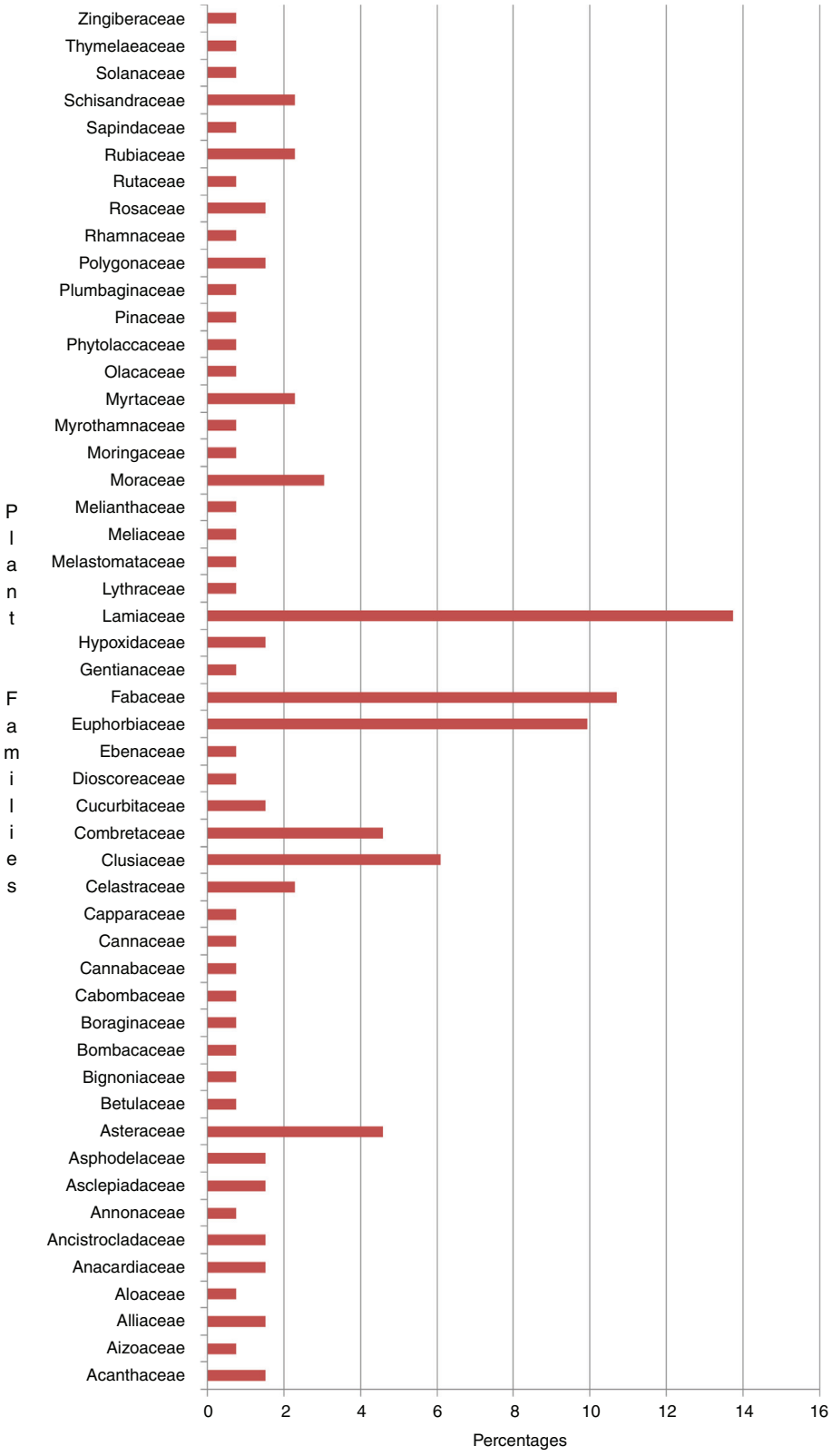


Fig. 1. Percentage frequency distribution of anti-HIV-1 RT plant species across families.

gallic acid, lupeol, luteolin (**9**), mangiferin (**3**), oleanolic acid, *p*-cymene, punicalin (**10**), rosmarinic acid, shikimic acid, stigmasterol, ursolic acid, xanthohumol (**11**), α-bergamotene (**2**), and γ-terpinene. Corollary to the principle that structure dictates function, it is unsurprising that these active compounds putatively inhibit or reduce the activity of RT, thus making HIV-infected cells produce fewer virions.

Pleiotropic effects

The second recurring motif is that numerous anti-HIV-1 RT phytochemicals enumerated in this review affect various targets and confer heterogenous pharmacological actions and health benefits. For example, andrographolide, a labdane diterpenoid produced by *A. paniculata* (Rao et al., 2004), has a broad range of therapeutic applications including anti-inflammatory, anti-platelet aggregation activities and potential antineoplastic properties (Burgos et al., 2005). Discovered in the leaves of the *A. korupensis* in Cameroon, michellamines are atropisomeric alkaloids with strong anti-HIV RT inhibitory activities (Manfredi et al., 1991; Vlietinck et al., 1998). They block HIV-induced cellular fusion and inhibit mutant HIV-1 RT. Michellamines are especially useful against RT from HIV-2 particularly found in and around Cameroon (Supko and Malspeis, 1994). In addition to their anti-HIV activities, michellamines have anti-parasitic and anti-leukaemic properties (Tshitenge et al., 2018). β-Amyrin, an oleanane-type pentacyclic triterpenoid, known to have many antiviral activities (Xiao et al., 2018), is also present in the genus *Moringa* (Rani et al., 2018).

Lupeol is a pharmacologically active triterpenoid endowed with several medicinal properties not least in colorectal cancer where it downregulates cell viability and activates cell apoptosis (Chen et al., 2018a,b). Parvez et al. (2018) reported that lupeol decreases the level of reactive oxygen species and restores antioxidant enzyme activities in the liver, and induces growth inhibition and apoptosis in a hepatocellular carcinoma cell line. Lupeol is a lead compound for the generation of more effective drugs against Influenza A and herpes simplex virus (Parvez et al., 2018). Isolated from *Guiera senegalensis*, a broad-spectrum African folk medicinal plant, lupeol (6.72 μg/mg) exerts anti-hepatitis B virus activity (Parvez et al., 2018).

HIV is associated with greater malaria mortality (Chintu et al., 1995) and acute malaria induces temporal increases in the HIV viral load (Vamvaka et al., 2014). HIV also triggers a wide range of opportunistic infections often misdiagnosed as malaria and HIV/malaria co-morbidity reduces the effectiveness of both antimalarial and antiretroviral drugs (Vamvaka et al., 2014). Given that co-administration of non-artemisinin antimalarial and antiretroviral drugs increases the risk of drug-related toxicity (Brentlinger et al., 2006), the action of artemisinin (**8**) on HIV-1 RT is noteworthy because its semi-synthetic derivatives can concurrently be used against HIV and *Plasmodium falciparum* malaria.

Corilagin is an ellagitannin first isolated in 1951 from *C. coriaria*. Apart from inhibiting HIV-1 RT, it also blocks hepatitis C virus (Reddy et al., 2018), attenuates allergy (Zhou et al., 2018a,b), and alleviates cholestasis (Yang et al., 2018a,b). Xanthohumol (**11**) is the main prenylated chalcone in the female inflorescences of *Humulus lupulus*, commonly known as hops. This hop-derived prenylated flavonoid has anticancer effects and significantly decreases age-related oxidative stress, inflammation and apoptosis as it regulates several pathways linked to proliferation and apoptosis (Fernández-García et al., 2018).

An ansamycin antibiotic originally isolated from the Ethiopian shrub *Maytenus serrata*, maytansine induces microtubule disassembly and disrupts mitosis (Kasilo et al., 2017). Since maytansine exhibits cytotoxicity against many tumour cell lines and inhibits tumour growth *in vivo*, it is an important antineoplastic and antimicrobial compound (Kusari et al., 2017). Hinokiflavone and other related biflavonoids including amentoflavone (**6**), robustaflavone, agathisflavone (**5**), rhusflavone and rhusflavanone are the cytotoxic principle of *Rhus succedanea* (Lin et al., 1989). These compounds are leading candidates in anti-HIV drug discovery (Parveen et al., 2018). In addition, hinokiflavone also has antioxidant and hepatoprotective effects (Zhou et al., 2018a,b; Abdel-Kader et al., 2018).

Putranjivain A possesses anti-herpes virus activity (Cheng et al., 2004). It also inhibits HIV attachment and penetration, and blocks late stage HIV replication. Mallotojaponin, a major constituent of pericarps of *Mallotus japonicas*, confers anticancer and anti-HIV effects (Satomi et al., 1994; Chauthe et al., 2012). β-Sitosterol is one of several phytosterols with anti-HIV activity. Since it significantly inhibits the growth of cancer cells without harming normal human cells (treatment with β-sitosterol triggers apoptosis as evidenced by caspase-3 and -9 activation), it is an important compound in the prevention and therapy of human cancers (Rajavel et al., 2018). The first flavone-xanthone *C*-glucoside, swertifrancheside, inhibits HIV-1 RT (Khan, 2017). This flavonoid is also an important lead in the discovery of anti-infective agents (Gautam et al., 2017).

Baicalein (**1**) is a flavone originally isolated from the roots of *Scutellaria baicalensis* and *Scutellaria lateriflora*. Besides its neuroprotective effects (Zhao et al., 2018a,b), baicalein suppresses the proliferation of human cervical cancer cells and induces apoptosis of liver cancer cells (He et al., 2018a,b; Lian et al., 2018). Betulinic acid is a naturally occurring pentacyclic triterpenoid which inhibits topoisomerase. It has antiretroviral, antimalarial, anti-inflammatory and anticancer properties (Li et al., 2018a,b,c; Kumar et al., 2018; Zhang et al., 2018). Cheng et al. (2018) found that 3-*epi*-betulinic acid isolated from two *Lithocarpus* species exerts strong anti-HIV activity comparable to abacavir, a drug used for treating HIV/AIDS. Gallic acid, also known as 3,4,5-trihydroxybenzoic acid, is a type of phenolic acid found in plants. Gallic acid, bergenin and quercitrin are used to treat pneumonia, cancer and HIV infection (Chen et al., 2018a,b; Prinsloo et al., 2018). An active green tea compound, epigallocatechin gallate (a type of catechin), also known as epigallocatechin-3-gallate, is the ester of epigallocatechin and gallic acid. In addition to inhibiting HIV-1-RT, epigallocatechin gallate inhibits Zika virus entry into host cells (Sharma et al., 2017a,b).

Ellagic acid is a polyphenolic antioxidant found in numerous plant foods including raspberries, strawberries, cranberries, walnuts, pecans and pomegranates. Since it inhibits HIV-1 infection *in vitro*, ellagic acid is a potential novel microbicide (Promsong et al., 2018). It has anti-proliferative (González-Sarrías et al., 2017) and antioxidant properties (Dalvi et al., 2017), prevents the destruction of the p53 gene by cancer cells (Ahire et al., 2017), and exerts anti-depressant-like actions (Bedel et al., 2017). Morosetti et al. (2017) report the use of ellagic acid in the chemoprevention of human papilloma virus-related pre-neoplastic lesions of the cervix. Ellagic acid also inhibits mutagenesis and carcinogenesis by forming adducts with DNA, thereby masking binding sites to be occupied by the mutagen or carcinogen. Nigranoic acid, a triterpenoid from *Schisandra sphaerandra*, inhibits HIV-1 RT (Khan, 2017) and its esters act as novel human neutrophil elastase inhibitors (Huang et al., 2015). Nigranoic acid protects against cerebral ischaemia–reperfusion injury (Feng et al., 2015).

Ursolic acid (ursane-type pentacyclic triterpenoid), also known as urson, prunol, micromerol or malol is one of the most promising therapeutic plant compounds with hepatoprotective activity and potent antiviral activity especially against herpes simplex virus and human hepatitis C virus (Parvez et al., 2018). Shikimic acid, commonly known by its anionic form shikimate, is an important biochemical intermediate in plants and microorganisms. It is a cyclohexene, a cyclitol and a cyclohexanecarboxylic acid; its name comes from the Japanese flower shikimi. Nabavi et al. (2018) reported that a shikimic acid rich extract of *Hypericum*

androsaemum presents protective effects during post-stroke depression, most likely due to antioxidant activity. Rosmarinic acid is an antioxidant and anti-inflammatory polyphenol found in a variety of plants. It improves learning and memory (Farr et al., 2016) but inhibits tumour-associated carbonic anhydrase isoenzymes and enzymes (Gülçin et al., 2016).

The terpinenes are a group of isomeric hydrocarbons that are classified as monoterpenes. A precursor of *p*-cymene, γ-terpinene is one of the three isomeric hydrocarbons with anti-HIV-1 RT actions. It is a natural antioxidant and anti-inflammatory agent isolated from a variety of plant sources including essential oils of citrus fruits (Ramalho et al., 2015). Myricetin is a member of the flavonoid class of polyphenolic compounds, with antioxidant properties and anti-HIV-1 RT activity (Pasetto et al., 2014). It is commonly derived from vegetables, fruits, nuts, berries, tea, and is also found in red wine (Đorđević et al., 2018). Naringenin, a bitter and colourless flavanone predominant in grapefruit, attenuates cART-induced sperm DNA fragmentations and testicular toxicity (Adana et al., 2018). Lim et al. (2018) found that naringenin protects pancreatic β-cells against oxidative stress-induced apoptosis.

Apart from inhibiting HIV-1 RT, the following active compounds also have other multiple effects. *N*-docosanol, a long chained alcohol, has anti-herpes simplex virus activity. It was approved by the FDA as a topical treatment for herpes simplex labialis (Hung et al., 2015). Flavonoids such as quercetin, isoquercitrin, rutin, hyperin, and quercitrin exhibit antimutagenic and free radical scavenging capacity (Hung et al., 2015). The phenolic compound chlorogenic acid has antipyretic and antibiotic activities (Hung et al., 2015). Tryptamine and ferulic acid significantly inhibit HIV-1 integrase (Sanna et al., 2018a,b). Smilarly, secocycloartanes are a class of triterpenoids with novel structures showing anti-HIV and anti-tumour activities (Li et al., 2017a,b). According to Rahim et al. (2018), cycloartane triterpenoids exhibit potent anti-proliferative activities against multidrug-resistant cancers and sub-micromolar anti-HIV activity.

Lectins are a ubiquitous group of carbohydrate-binding proteins. Some of the microbial and plant lectins are griffithsin, actinohivin, concanavalin-A, cyanovirin-N, microvirin, and banana lectin (BanLec). During HIV infection, opportunistic pathogens including enveloped viruses, bacteria, fungi, and protozoa are neutralized by lectins because they display sugar-coated macromolecules on their surfaces, making them suitable targets for lectins (Mazalovska and Kouokam, 2018). Emetine is an FDA approved drug for amoebiasis and several viruses. Cephaeline, a structural desmethyl emetine analogue, inhibits Zika virus polymerase activity and Ebola virus entry (Yang et al., 2018a,b).

Nitidine is a bioactive plant benzophenanthridine alkaloid with marked anticancer, neuroprotective, antimalarial, anti-HIV, analgesic, anti-inflammatory, and antifungal activities (Khan et al., 2018). Despite its outstanding therapeutic potential, it has not yet been subjected to clinical trials (Khan et al., 2018). Schisandrin B and deoxyschisandrin and other lignans with a dibenzocyclooctadiene skeleton have antihepatotoxic, antiasthmatic, and anti-tumour effects (Su et al., 2018). Wikstroelides (daphnane diterpenes) inhibit hepatitis B virus (Li et al., 2018a,b,c). Curcuminoids have anti-inflammatory, antioxidant, anticancer, and anti-HIV-1 integrase activities (Cunha Neto et al., 2018). As noted in many of the cases, anti-HIV-1 RT active compounds have a multiplicity of pleiotropic pharmacological effects and benefits during infection and disease.

Towards the development of plant-derived anti-HIV-1 RT drugs

Fig. 2 shows pillars for the discovery and development of anti-HIV-1 RT inhibitors from plants. On one hand, the pillars act as drivers, prerequisite technical knowledge and conditions that can initiate, support and accelerate the discovery and development of plant-derived anti-HIV-1 RT inhibitors from plants. On the other, the pillars also act as bottlenecks, namely critical resources whose inefficiencies create delays, limit the throughput or impede the research and development process from progressing. To accelerate drug discovery and development, this review considers four important pillars: tapping into the rich vein of indigenous knowledge of putative anti-HIV/AIDS medicinal plants (reverse pharmacology), determining pan-assay interference compounds, analysis of structure–activity relationships, and conducting more clinical trials.

Reverse pharmacology

About 21 drugs sold in 2007 to treat HIV-1 infection were all obtained by chemical synthesis, and none from natural products (Chinsembu, 2016). Yet, indigenous knowledge, coupled with a history of safe use and ethnopharmacological efficacy, present a faster approach to discover new anti-HIV-1 agents from plants. This new approach, now called reverse pharmacology (Chinsembu, 2009), is a trans-disciplinary approach focused on indigenous knowledge of medicinal plants, experimental observations and clinical experiences (Simoes-Pires et al., 2014). Reverse pharmacology promises to shorten the classical drug discovery process (Chinsembu, 2016). Tapping into the rich vein of ethnobotanical knowledge can unveil putative plant medicines that could provide crucial and quick leads to the development of new drugs against HIV-1 RT.

Plants continue to be a very important resource for HIV/AIDS remedies and beneficial compounds. In fact, given rampant drug shortages in poor countries, even qualified western-trained medical doctors sometimes prescribe herbal remedies for the management of HIV/AIDS (Chinsembu, 2016). In many resource-poor settings, various plants used to treat HIV-1 infection have known anti-RT activity. In Ethiopia, acetone extracts from the plant *Combretum molle* inhibit HIV-1 RT (Asres and Bucar, 2005). Phytochemical investigations of this fraction showed that the HIV-1 RT inhibitory properties are mediated by two tannins and two oleanane-type pentacyclic triterpene glycosides. A natural agent, gallotannin, isolated from *C. molle*, inhibits RDDP activity of HIV-1 RT. Similar results were obtained in South Africa where the methanol extract of the roots of *C. molle* had the highest inhibitory effect on the RNase H activity of HIV-1 RT (Bessong et al., 2005).

L-Canavanine from *Sutherlandia frutescens* has activity against HIV but synergistically interacts with the efflux of nevirapine (Prinsloo et al., 2018). D-Pinitol, also from *S. frutescens*, has been suggested as a treatment for wasting in cancer and AIDS patients. Recent evidence shows that D-pinitol, chemically known as 3-*O*-methyl-D-chiro-inositol, is an active ingredient of *Diospyros mespliformis* leaves, whose crude extracts inhibit HIV (Chinsembu, 2016). D-Pinitol is also known to possess anti-diabetic activity. Catechin (a flavonoid), bergenin (a *C*-galloyl-glycoside) and betulinic acid have been isolated from *Peltophorum africanum*, an important southern African ethnomedicinal plant for HIV/AIDS (Chinsembu, 2015; 2016).

In South Africa, Bessong et al. (2005) screened seventeen aqueous and methanol extracts of nine South African medicinal plants. The plants were ethnobotanically selected and evaluated for inhibitory properties against HIV-1 RT. Inhibitory action was seen with the stem-bark of *P. africanum* (IC_{50} 3.5 μg/ml) and the roots of *C. molle* (IC_{50} 9.7 μg/ml). Extracts of the leaves of Sudanese plant *Combretum hartmannianum* totally inhibits HIV-1 RT at a concentration of 66 μg/ml (Ali et al., 2002). Other experiments by Chukwujekwu et al. (2014) attest that *Centratherum punctatum* leaves have HIV-1 RT inhibitory activity (IC_{50} = 52.4 μg/ml). The plant *C. punctatum* is commonly known as the Brazilian bachelor button, a refreshing pineapple-scented bushy perennial plant. In Brazilian traditional medicine, it is used as a treatment for heart

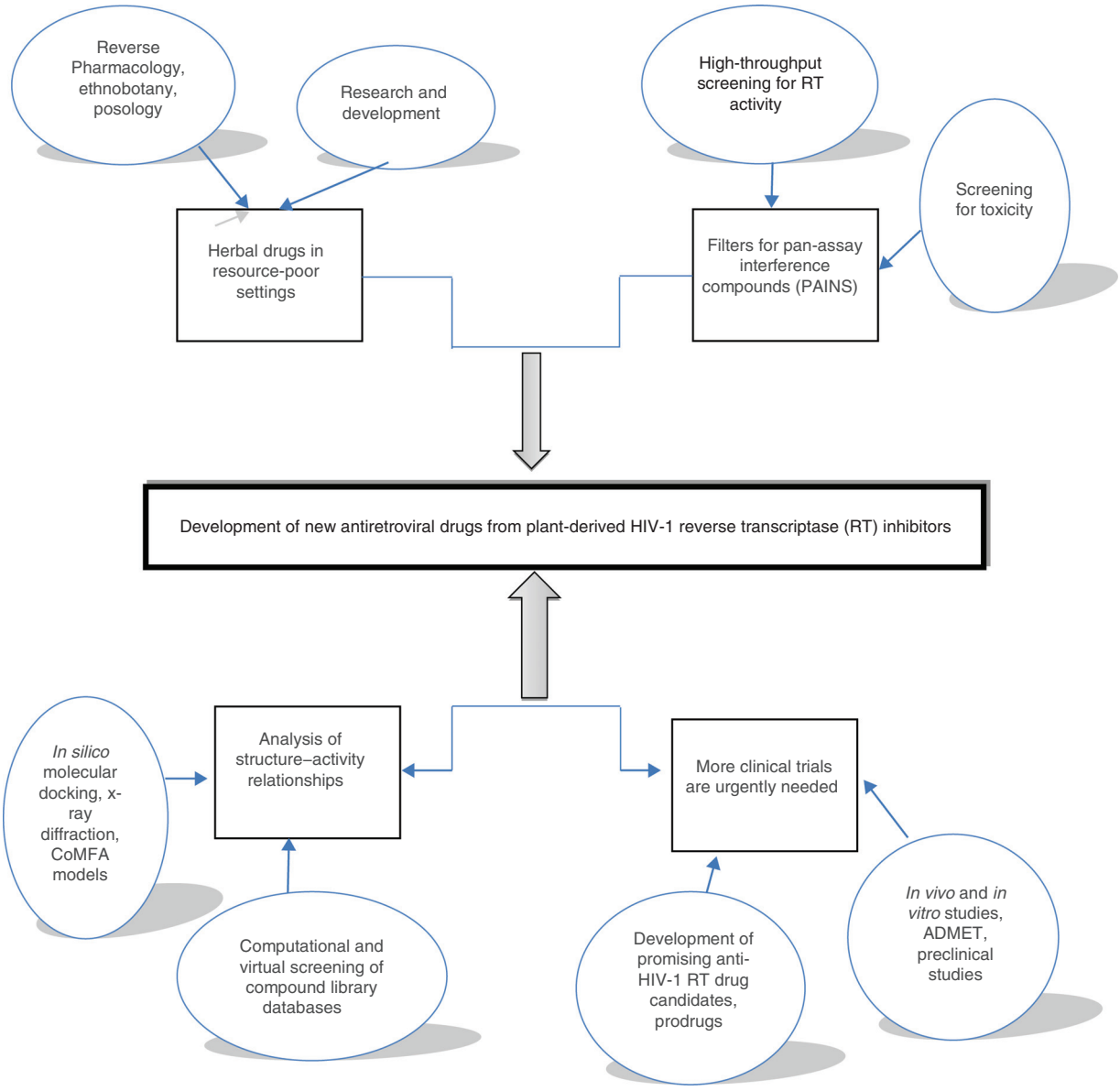


Fig. 2. Pillars for the development of plant-derived HIV-1 RT inhibitors.

ailments. Its leaves have antimicrobial, antioxidant and antiproliferative properties (Chukwujekwu et al., 2014).

Woradulayapinij et al. (2005) studied the *in vitro* HIV-1 RT inhibitory activities of Thai medicinal plants. They tested water and 80% ethanol extracts of twenty Thai medicinal plants used to treat AIDS for their HIV-1 RT inhibitory activity. The water extracts of *Ipomoea carnea* subsp. *fistulosa* (aerial parts), *Vitex glabrata* (branch), *Vitex trifolia* (aerial part), *Vitex negundo* (aerial part), *Canna indica* (rhizome), and *Justicia gendarussa* (aerial part) showed HIV-1 RT inhibition ratio higher than 90% at a 200 μg/ml concentration. Although *T. sericea* wields very strong activity against the HIV-1 RDDP and RNase H with 98% and 99% inhibition, respectively (Bessong et al., 2004), the plant may contain high levels of toxic tannins (Ndhlala et al., 2013; Wink and Van Wyk, 2008). In experiments performed in Tanzania, Moshi and Mbwambo (2005) observed that, with the exception of the dichloromethane and petroleum ether extracts, all the intermediate and polar extracts of *T. sericea* were toxic with values ranging from 5.4 to 17.4 mg/ml. This result suggests that plants that show anti-HIV-1 RT activity should also be evaluated for cytotoxicity.

Although Africa has the highest burden of HIV/AIDS, few scientific studies that screen plants for anti-RT activity are conducted on the continent (Chinsembu, 2016). Primary data on chemical diversity and activity profiles of HIV-1 RT inhibitors from plants are mostly available from studies done outside Africa. Whereas the Chinese represent about 41% of all research efforts on anti-HIV natural products, the African share of research on anti-HIV natural products is a paltry 16% (Chinsembu, 2016). Most of the studies done in Africa are ethnobotanical and are inconclusive. While Sub-Saharan Africa accounts for about 70% of all HIV infections, it is ironic that the search for novel anti-HIV-1 RT treatments and the hotbeds of research and development for anti-HIV-1 RT plants are in China where HIV prevalence rate is less than 0.1% among adult (Chinsembu, 2016).

Africa is not investing enough of her resources in the search for new anti-HIV-1 RT inhibitors from plants. This means that Africa will continue to look to the outside world for novel drugs to manage HIV/AIDS. Africa has failed to sow the seed of self-reliance in terms of searching for new plant remedies to combat HIV/AIDS. This is disheartening considering that Africa is endowed with abundant

Box 1
Chemical diversity and activity profiles of HIV-1 reverse transcriptase inhibitors from plants.

Species	Family	Phytochemical diversity	Reverse transcriptase inhibitory profiles	References
Andrographis paniculata Nees	Acanthaceae	Aqueous extracts of leaves contain a bicyclic *ent*-labdane type diterpene lactone, andrographolide	Water extracts show EC_{50} values from 4.2 to 175 μg/ml	Narayan et al. (2013), Otake et al. (1995)
Justicia gendarussa Burm.f.	Acanthaceae	Justiprocumins A and B, new arylnaphthalide lignans (ANL) glycosides; the ANL patentiflorin A has significantly higher RT inhibitory effect than AZT, even against drug-resistant HIV-1 isolates	Aerial part shows RT inhibition ratio higher than 90% at a 200 μg/ml concentration	Zhang et al. (2017a,b), Woradulayapinij et al. (2005)
Sceletium tortuosum (L.) N.E.Br.	Aizoaceae	Anthraquinones, terpenes, polyphenols, anthocyanin, tannins, alkaloids, glycosides, carbohydrates and coumarins	RT inhibition testing showed IC_{50} values of <50 and 121 μg/ml for ethanol and ethyl acetate extracts, respectively	Kapewangolo et al. (2016a,b)
Allium sativum L. *Allium ascalonicum* L.	Alliaceae	About 80% inhibition of RT; antifungal peptide called ascalin, a 9.5-kDa chitinase-like peptide present in bulbs of *A. ascalonicum* inhibits RT	IC_{50} = 10 μM	Silprasit et al. (2011), Wang and Ng (2002)
Aloe chabaudii Schönland	Aloaceae	Total phenolics, flavonoids, gallotannin, condensed tannin	Root water extract, IC_{50} = 0.6 ± 0.06 mg/ml	Mulaudzi et al. (2011)
Rhus succedanea L.	Anacardiaceae	Eleven bioflavonoids including robustaflavone and hinokiflavone; these two bioflavonoids had similar activity against RT; other biflavonoids were amentoflavone (**6**), agathisflavone (**5**) and morelloflavone	IC_{50} = 65 μM for robustaflavone and hinokiflavone; IC_{50} values for other biflavonoids were: amentoflavone, 119 μM; agathisflavone, 100 μM; and morelloflavone, 116 μM	Lin et al. (1997)
Amphipterygium glaucum (Hemsl. & Rose) Hemsl. & Rose ex Standl.	Anacardiaceae	Triterpenes	IC_{50} = 59.25–97.83 μg/ml against HIV-RT; low toxicity to macrophages of <23.8%	Gómez-Cansino et al. (2015)
Ancistrocladus korupensis D.W.Thomas & Gereau *Ancistrocladus heyneanus* Wall. *Ancistrocladus congolensis* J.Léonard	Ancistrocladaceae	Michellamines A and B, RT activity for michellamine B Betulinic acid, a naturally occurring pentacyclic triterpene belonging to the lupane family Michellamines A_2, A_3, A_4, B	EC_{50} = 1 μM IC_{50} = 8–13 μM IC_{50} = 29.6 μM, 15.2 μM, 35.9 μM, 20.4 μM, respectively	Narayan et al. (2013), Singh et al. (2005) Kuo et al. (2009), Yogeeswari and Sriram (2005), Pengsuparp et al. (1995) Bringmann et al. (2016)
Uvaria angolensis Welw. ex Oliv.	Annonaceae	Glycosides, chalcone derivatives, angoletin (**7**) compound, two monoacyl glycerols such as 1-palmitoyl and stearyl glycerol; stem bark methanol extract inhibits both HIV-1 RNase H function and RDDP activity; angoletin inhibits RNase H and RDDP, respectively; water fraction isalso endowed with anti-RNase H activity	Stem bark methanol extract inhibits both HIV-1 RNase H function and RDDP activity with IC_{50} values of 1.0 ± 0.2 and 0.62 ± 0.15 μg/ml, respectively; angoletin showed an IC_{50} of 0.10 ± 0.03 and of 0.23 ± 0.04 μg/ml against RNase H and RDDP, respectively; water fraction endowed with anti-RNase H activity below 1 μg/ml and no cytotoxic effect	Ngoutane Mfopa et al. (2018)
Hemidesmus indicus (L.) R.Br.	Asclepiadaceae	Lupeol, lupeol acetate, 2-hydroxy-4-methoxybenzaldehyde, 3-hydroxy- 4-methoxybenzaldehyde and 2-hydroxy-4-methoxybenzoic acid, caffeic acid, chlorogenic acid and β-amyrin acetate; decoction inhibits RT-associated RNase H and RDDP	Lupeol (IC_{50} = 3.8 μM), lupeol acetate (IC_{50} = 6.4 μM), chlorogenic acid and β-amyrin acetate (IC_{50} = 4.7 μM); decoction inhibits RT-associated RNase H function and RDDP; IC_{50} values around 3 and 7 μg/ml for RNase H and RDDP functions	Esposito et al. (2017)
Hoodia gordonii (Masson) Sweet ex Decne.	Asclepiadaceae	Glycosides, phenolics, alkaloids, tannins and terpenes, *H. gordonii* extract demonstrated good inhibition against HIV RT for ethanol and ethyl acetate extracts	IC_{50} values of 73.5 and 69.8 μg/ml for ethanol and ethyl acetate extracts, respectively	Kapewangolo et al. (2016a,b)
Bulbine frutescens Willd. *Bulbine alooides* Willd.	Asphodelaceae	Phenols, alkaloids and flavonoids; ethyl acetate fraction reconstituted in dimethyl sulfoxide crude extract inhibits RT Tannins; water and ethanol root extracts inhibit RT	IC_{50} = 0.52 ± 0.03 mg/ml Water and ethanol root extracts inhibit RT by ≥50%	Shikalepo et al. (2017) Klos et al. (2009)
Parthenium hysterophorus L.	Asteraceae	Sesquiterpene lactones, hysterin, ambrosin, flavonoids such as quercelagetin 3,7-dimethylether, 6-hydroxyl kaempferol 3-*O*- arabinoglucoside, fumaric acid, *p*-hydroxybenzoic acid and vanillic acid, caffeic acid, *p* courmaric, anisic acid, *p*-anisic acid, chlorogenic acid, ferulic acid, sitosterol and some unidentified alcohols	About 40% inhibition of RT activity was observed in hexane fraction in anti-HIV assay at 6.0 μg/ml concentration	Kumar et al. (2013), Patel (2011)

Box 1 (*Continued*)

Species	Family	Phytochemical diversity	Reverse transcriptase inhibitory profiles	References
Centratherum punctatum Cass.	Asteraceae	Germacranolide sesquiterpene lactones, centratherin and its derivative isocentratherin; crude extract exhibit RT inhibitory activity	IC_{50} = 72.8 μg/ml; remarkable RT inhibitory activity, IC_{50} = 52.4 μg/ml, observed with dichloromethane fraction	Chukwujekwu et al. (2014)
Vernonia stipulacea Klatt	Asteraceae	Gallic acid, chlorogenic acid, dicaffeoyl acids, quercetin, vernolide, vernodalin, vernodalinol, vernonioside A3, octahydroverdalin	Weak RT activity of >100 μg/ml; RDDP IC_{50} = 350 μg/ml for methanol extract; the methanol extract stimulates RT activity at 100 μg/ml	Prinsloo et al. (2018), Bessong et al. (2005)
Artemisia annua L.	Asteraceae	Artemisinin (**8**)	IC_{50} 100 μM (Tietjen et al., 2016) stated that EC_{50} value of 20.9 μg/ml for *A. afra* confirms previously reported IC_{50} values in the range of 1.0–48.0 μg/ml repoted by Lubbe et al. (2012)	Tietjen et al. (2016), Lubbe et al. (2012), Singh et al. (2005)
Petasites japonicus F.Schmidt	Asteraceae	Sesquiterpenes and a carcinogenic compound called petasitenine (a new pyrrolizidine alkaloid) have been isolated from young flower stalks; also contains fukinone and eremophilenolides, including a mixture of two new compounds 6β-angeloyloxy-3β,8α-dihydroxyeremophil-7(11)-en-12,8β-olide and 6β-angeloyloxy-3β,8β-dihydroxyeremophil-7(11)-en-12,8α-olide; ethanol and water extracts inhibit both RDDP and RNase H of RT	EC_{50} values of 1–2 μg/ml	Hisayoshi et al. (2015), Sugama et al. (1985), Hirono et al. (1977)
Onopordum illyricum L.	Asteraceae	Luteolin (**9**), apigenin, hispidulin, arctiin, 1,5-dicaffeoylquinic acid (**4**), and two germacranes, 8α-(5-hydroxy)-angeloylsalonitenolide and onopordopicrin	Luteolin is the most effective on RNase H RT-associated function (IC_{50} of 12.8 μM), followed by 1,5-dicaffeoylquinic acid and apigenin with IC_{50} values of 16.9 and 59.6 μM, respectively	Sanna et al. (2018a,b)
Alnus firma Siebold & Zucc.	Betulaceae	Terpenoids, flavonoids, diarylheptanoids, phenols, steroids, tannins; luteolin 7,4′-dimethyl ether; myricetin 3-*O*-β-D-galactopyranoside displayed inhibition against HIV-1 RT	IC_{50} values of 60 mM	Sati et al. (2011)
Kigelia africana (Lam.) Benth.	Bignoniaceae	Flavonoids and phenolics, iridoids and limonoids, phenyl ethanoglycosides and naphthoquinones, terpenes, terpenoids and steroids, meroterpenoid naphthoquinones, iridoid glycosides and phenylpropanoid/eucommiol derivatives, coumarins, lignans; weak RT inhibition of 33.1% by a 100 μg/ml leaf extract; even weaker is the fruit extract	13.2% RT inhibition at 100 μg/ml	Osman et al. (2017), Bello et al. (2016), Rukunga et al. (2002)
Adansonia digitata L.	Bombacaceae	Terpenoids, flavonoids, sterols, vitamins, amino acids, carbohydrates, and lipids; flavonoid glycosides, proanthocyanidin compounds, epicatechin	80% methanol stem bark extract, IC_{50} = 2.3 μg/ml; IC_{50} = 0.1 ± 0.01 mg/ml for bark water extract	Sharma and Rangari (2016), Mulaudzi et al. (2011)
Lobostemon trigonus H.Buek	Boraginaceae	Naphthoquinone derivatives, pyrrolizidine alkaloids, cyclitols, phenolic acids, and tannins; leaf extracts contain a potent RT inhibitor	IC_{50} value of 49 μg/ml	Prinsloo et al. (2018), Harnett et al. (2005)
Brasenia schreberi J.F.Gmel.	Cabombaceae	15 polyphenols including gossypetin and hypolaetin 7-*O*-glucoside weakly inhibit HIV-1 RT activity; ethanol and water extracts inhibit both DNA polymerase and RNase H of RT	EC_{50} values of 1–2 μg/ml	Hisayoshi et al. (2015)
Humulus lupulus Thunb.	Cannabaceae	Xanthohumol (11), a prenylchacone flavonoid, inhibits RT	EC_{50} = 0.50 μg/ml; therapeutic index = 10.8	Wang et al. (2004)
Canna indica L.	Cannaceae	Active proteins Cip31 (31 kDa) and Cip14 (14 kDa)	IC_{50} of 17.41 and 19.25 μg/ml, respectively	Woradulayapinij et al. (2005)
Capparis spinosa L.	Capparaceae	Kaempferol 3-rhamnosyl-rutinoside, kaempferol 3-rutinoside and quercetin 3-rutinoside, rutin (quercetin-3-*O*-rutinoside), benzofuranone enantiomers 2-(4-hydroxy-2-oxo-2,3-dihydrobenzofuran-3-yl)acetonitrile, *p*-hydroxybenzoic acid, vanillic acid, protocatechuric acid, butanedioic acid, uracil, uridine and daucosterol; protein similar to imidazoleglycerol phosphate synthase has RT inhibitory activity	IC_{50} of 0.23 μM	Zhang and Ma (2018), Lam and Ng (2009)
Maytenus buchananii (Loes.) R.Wilczek	Celastraceae	Triterpenes, phenolic glucosides, flavonoids and alkaloids such as maytansine, maytanprine and maytanbutine	Stem bark water extract inhibits RT by 95%	Tebou et al. (2017), Rukunga et al. (2002)

Box 1 (*Continued*)

Species	Family	Phytochemical diversity	Reverse transcriptase inhibitory profiles	References
Elaeodendron schlechterianum Loes. *Elaeodendron transvaalense* (Burtt Davy) R.H.Archer	Celastraceae	Cardiac glycosides and tannins, 3-oxo-28-hydroxylbetuli-20(29)-ene and 3,28-dihydroxylbetuli-20(29)-ene; cardiac glycoside, digitoxigenin-3-*O*-glucoside, is the main anti-HIV agent	RNase H IC_{50} = 31.2 μg/ml for water extract	Maregesi et al. (2010), Bessong et al. (2005)
Garcinia multiflora Champ. ex Benth *Garcinia speciosa* Wall *Garcinia nuntasaenii* Ngerns. & Suddee	Clusiaceae	Biflavonoids including amentoflavone (**6**), agathisflavone (**5**), robustaflavone, hinokiflavone, volkensiflavone, morelloflavone, rhusflavanone; robustaflavone and hinokiflavone inhibit RT Protostanes, garcisaterpenes A and C; four benzophenones (garciosones A–D), four xanthones (garciosones E–H) and three biphenyls (garciosines A–C); 2-(3,3-dimethylallyl)-1,3,7-trihydroxyxanthone was the most active compound RT assay Polycyclic polyprenylated acylphloroglucinols (garcinuntins A–C), biphenyl derivatives (garcinuntabiphenyls A–C) and a lanostane triterpene (garcinuntine) were isolated from the root; while compounds garcinuntin B, garcinuntabiphenyl C, 2-deprenyl-rheediaxanthone B, morelloflavone and volkensiflavone showed anti- RT activity; the compound 1,3,6,7-tetrahydroxyxanthone or mangiferin (**3**) exhibited the most potent anti-RT activity with comparable activity to that of fagaronine chloride	Robustaflavone and hinokiflavone inhibit RT with IC_{50} of 65 μM Protostanes, garcisaterpenes A and C, EC_{50} = 5.8 μg/ml 2-(3,3-dimethylallyl)-1,3,7-trihydroxyxanthone was the most active compound RT assay, IC_{50} = 58.24 μM Morelloflavone and volkensiflavone showed anti-RT activity with IC_{50} values in the range of 86.94 to 202.50 μM; mangiferin exhibited the most potent anti-RT activity with comparable activity to that of fagaronine chloride, IC_{50} = 28.25 μM, and garcinuntine inhibits RT with IC_{50} >45 μM	Singh et al. (2005), Lin et al. (1997) Pailee et al. (2018) Chaturonrutsamee et al. (2018)
Calophyllum inophyllum L. *Calophyllum brasiliense* Cambess.	Clusiaceae	Coumarins, xanthones, flavonoids and triterpenes; pyranocoumarins and inophyllums such as caloinophyllin A, inophyllum B, nobiletin, pentamethylquercetin and inophyllum B Triterpenes such as oleanolic acid; masticadienonic acid, 3-hydroxymasticadienonic acid, and 3-hydroxymasticadienonic acid; apetalic acid, calanolide B and C and soulatrolide inhibit RT; apetalic acid and calanolides B and C are potent RT inhibitors	Inophyllum B inhibits RT non-competitively with a Ki of 42 nM; IC_{50} = 1.5 μM Oleanolic acid, IC_{50} = 3.1 μM; masticadienonic acid, 3-hydroxymasticadienonic acid, and 3-hydroxymasticadienonic acid; apetalic acid, calanolide B and C and soulatrolide inhibit RT (IC_{50} 26.24–35.17 μg/ml); apetalic acid and calanolides B and C are RT inhibitors, IC_{50} = 20.2 μg/ml	Ponguschariyagul et al. (2018), Laure et al. (2008), Taylor et al. (1994), Patil et al. (1993) Gómez-Cansino et al. (2015), César et al. (2011), Akihisa et al. (2001)
Vismia cayennensis (Jacq.) Pers.	Clusiaceae	Anthraquinones, prenylated benzophenones	Vismiaphenone D has EC_{50} = 11 μg/ml	Singh et al. (2005), Fuller et al. (1999)
Hypericum hircinum L.	Clusiaceae	Essential oils from aerial parts are dominated by sesquiterpene hydrocarbons such as *cis*-β-guaiene, δ-selinene and (*E*)-caryophyllene, while the non-volatile leaf extract contains chlorogenic acid, quercetin, mangiferin (**3**), and biagenin but lacks hypericin; betulinic acid, shikimic acid, chlorogenic acid, 5,7,3′,5′-tetrahydroxyflavanone, and 5,7,3′,5′-tetrahydroxyflavanone 7-*O*-glucoside	Shikimic acid, IC_{50} as low as 2 μg/ml; quercetin's RNase H IC_{50} = 4.5 μM; betulinic acid has IC_{50} of 2 μM on RNase H	Ornano et al. (2018), Esposito et al. (2013)
Cratoxylum arborescens (Vahl) Blume	Clusiaceae	Betulinic acid, lupenediol and lupenoic acid	IC_{50} = 10.8, 14.0, and 8.7 μg/ml, respectively	Cassels and Asencio (2011)
Combretum molle Engl. & Die *Combretum hartmannianum* Schweinf.	Combretaceae	Gallotannin, ellagitannin, pentacyclic triterpene glucosides like punicalagin, arjunglucoside and sericoside	Stem bark aqueous extract inhibits RDDP by 58%, IC_{50} = 81.3 μg/ml; stem bark aqueous extract inhibits RNase H function by 64%; stem bark methanol extract, IC_{50} for RNase H = 21.6 μg/ml; methanol extract of the roots, RNase H activity, IC50 9.7 μg/ml Extracts of the leaves of *C. hartmannianum* totally inhibit the enzyme RT at a concentration of 66 μg/ml	Bessong et al. (2004) Ali et al. (2002)

Box 1 (*Continued*)

Species	Family	Phytochemical diversity	Reverse transcriptase inhibitory profiles	References
Terminalia chebula Willd. ex Flem. *Terminalia sericea* Burch. ex DC. *Terminalia catappa* L.	Combretaceae	Gallic acid and galloyl glucoses; chebulagic acid and chebulinic acid Triterpenoids, saponins, tannins, anolignan B; Tannins, gallotannins, ellagitannins, cyanidin, and flavonoids like cyanidins, proanthocyanidin, flavonols and flavononols; gallic acid and its derivatives like ethyl and methyl gallate, chebulagic and chebulinic acid, tetra and penta-galloylglucose; gallo- and ellagi-tannins such as 1,3,4-tri-*O*-galloylquinic acid, 3,5-di-*O*-galloyl-shikimic acid, 3,4,5-tri-*O*-galloylshikimic acid, punicalin (*10*), punicacortein and punicalagin	IC_{50} ≤50 μg/ml Methanol extract strongly inhibits RDDP (IC_{50} = 7.2 μg/ml) and the ribonuclease H, IC_{50} = 8.1 μg/ml Punicalin and punicacortein C inhibit purified HIV RT with ID_{50} of 8 μM and 5 μM, respectively	Bessong et al. (2005) El-Mekkawy et al. (1995) Mahmood et al. (2018), Dwevedi et al. (2016), Eldeen et al. (2011)
Anogeissus acuminata (Roxb. ex DC.) Wall. ex Guillem. & Perr.	Combretaceae	Anolignan A and B	Anolignan A, IC_{50} of 156.9 μg/ml against HIV-2 RT; also showed moderate inhibitory activity against a drug-resistant form of HIV-1 RT with IC_{50} of 106.0 μg/ml; in other studies, anolignan A showed IC_{50} = 60.4 μg/ml; anolignan B showed IC_{50} = 1072 μg/ml	Singh et al. (2005), Rimando et al. (1994)
Momordica charantia Descourt.	Cucurbitaceae	Glycosidic compounds, cucurbitane glucoside, momordicine, triterpene glycosides, cucurbitane-type triterpenoids, iridoid lactone and α-and β-momorcharin; *Momordica* anti-HIV protein (MAP30); lectins; Kuguacins A–E, belong to family of cucurbitacins; lectins and MAP30 inhibit RT; protein (MRK29) isolated from ripe fruit and seed at the concentration of 18 mg/ml showed RT inhibition ratio of 50%	Cucurbitacins, IC_{50} = 28 μM	Palamthodi and Lele (2014), Kuo et al. (2009), Akihisa et al. (2001)
Coccinia rehmannii Cogn.	Cucurbitaceae	Unknown compounds	Inhibit RT by at least 40%	Sigidi et al. (2017)
Dioscorea bulbifera L.	Dioscoreaceae	Quercetin, kaempferol, sitosterol-β-D-glucoside, (+)-catechin, diosbulbin E acetate, and lectins; a mannose binding lectin showed strong anti-RT activity;	One novel lectin inhibited RT with an IC_{50} of 0.93 μM; a trypsin-stable lectin inhibted RT with IC_{50} = 73 μM	Sharma et al. (2017a,b), Chaniad et al. (2016), Li et al. (2008), Wong and Ng (2003)
Diospyros mespiliformis Hochst. ex A.DC.	Ebenaceae	Tannins, steroids, anthocyanins and flavonoids; root extracts showed 17.4% inhibition RT; D-Pinitol rich leaf extract	D-Pinitol rich leaf extract at 0.1 mg/ml had 78.7% RT inhibitory activity	Mamba et al. (2016)
Phyllanthus niruri Roxb. ex Wall. *Phyllanthus pulcher* (Baill.) Wall. ex Müll.Arg. *Phyllanthus urinaria* Wall. *Phyllanthus emblica* L. *Phyllanthus amarus* Schumach. & Thonn. *Phyllanthus reticulatus* Poir.	Euphorbiaceae	Corilagin, gallic acid, flavonoids, alkaloids, terpenes and lignans; main RT inhibitor is repandusinic acid A (RA); approx. 10-fold more sensitivity to RT than DNA polymerase α; niruside has anti-RT activity Terpenoids, phenylpropanoids, tannins, flavonoids, alkaloids, phenols A variety of compounds including polyphenols, tannins, lignans, triterpenoids, flavonoids and alkaloids; flavonoids such as astragalin, quercetin, quercitrin, isoquercitrin, rutin and kaempferol; triterpenes like lupeol acetate and β-amyrin; sterols like daucosterol and β-sitosterol; coumarins such as trimethylester dehydrochebulic acid, methylbrevifolin carboxylate and ellagic acid; gallic acid, a major polyphenol compound, inhibits RT 1, 6-di-*O*-galloyl-β-D-glucose, 1-*O*-galloyl-β-D-glucose, kaempferol-3-*O*-β-D-glucoside, quercetin-3-*O*-β-D-glucoside, digallic acid and putranjivain A Aqueous and ethanolic extracts rich in corilagin	Main RT inhibitor is RA; ID_{50} of RA on RT and DNA polymerase α were 0.05 μM and 0.6 μM, respectively; approx. 10-fold more sensitivity to RT than DNA polymerase α Strong inhibition of RT was obtained by *P. pulcher* (IC_{50} 5.9 μg/ml) followed by *P. urinaria* and *P. myrtifolius*, IC_{50} of 10.4 and 12.7 μg/ml, respectively Gallic acid, IC_{50} = 0.76 μg/ml; binding rate 37%; polyphenol extract, IC_{50} = 0.61 μg/ml, 66% binding rate Most potent compound is putranjivain A, IC_{50} = 3.9 μM IC_{50} = 8.17 μg/ml (Notka et al., 2003) reported IC_{50} values from 1.8 to 14.6 μg/ml; inhibition of RNase H activity by 99% and 98%, respectively; 50 μg/ml of the methanol extracts of leaves and stem of ***P. reticulatus*** were the most active against RNase H, with inhibition of 99% and 96%, respectively	Eldeen et al. (2011), Ogata et al. (1992) Zhang et al. (2017a,b), Mao et al. (2016) Calixto et al. (1998), El-Mekkawy et al. (1995) Akram et al. (2018) Notka et al. (2003), Tai et al. (2011), Notka et al. (2003)
Mallotus philippensis (Lam.) Mull.Arg.	Euphorbiaceae	Phenols, diterpenoids, steroids, flavonoids, cardenolides, triterpenoids, coumarins, isocoumarins, bergenin, mallotophilippinens, rottlerin, isorottlerin, and phloroglucinol derivative called mallotojaponin is a competitive RT inhibitor	Mallotojaponin is a competitive RT inhibitor with Ki value of 6.1 μM; no RT acivity in study by Silprasit et al. (2011)	Gangwar et al. (2014), Silprasit et al. (2011), Nakane et al. (1991)

Box 1 (*Continued*)

Species	Family	Phytochemical diversity	Reverse transcriptase inhibitory profiles	References
Euphorbia hirta L.	Euphorbiaceae	Triterpenes, phytosterols, tannins, alkanes, polyphenols and flavonoids	IC_{50} = 73 μg/ml for 80% methanol extract; 27 μg/ml for water extract	Gyuris et al. (2009)
Euphorbia characias Sm.		Phenolic compounds including flavonoids; organic extracts inhibit HIV-1 RT-associated RDDP and RNase H functions	IC_{50} = 0.2 μg/ml	Pisano et al. (2016)
Croton echinocarpus Baill.	Euphorbiaceae	Two alkaloids: corydine and norisoboldine	Both alkaloids have significant *in vitro* anti-HIV potential, inhibiting 40% of the HIV-1 RT activity at a concentration of 100 μg/ml of norisoboldine and 450 μg/ml of corydine; corydine, IC_{50} = 356.8 μg/ml, norisoboldine, IC_{50} = 153.7 μg/ml	Ravanelli et al. (2016)
Alchornea cordifolia (Schumach.) Müll.Arg.	Euphorbiaceae	Tannins, phenolic acids such as gallic acid, ellagic acid, protocatechuic acid, flavonoids including quercetin, hyperin and guaijaverin, some imidazopyrimidine alkaloids named as alchorneine, alchornidine and several guanidine alkaloids, six terpenoids notably stigmasterol, stigmasta-4,22-dien-3-one, friedelin, friedelane-3-one-28-al, 3-*O*-acetyl-erythrodiol and 3-*O*-acetyl-aleuritolic acid as well as a phenolic acid called methyl-3,4,5-trihydroxybenzoate	Aqueous seed extract inhibited HIV-1 RT activity at EC_{50} values of <0.01–0.03 mg/ml	Boniface et al. (2016), Ayisi and Nyadedzor (2003)
Bridelia micrantha Baill.	Euphorbiaceae	Flavonoids, tannins, friedelin, phenolic derivatives such as gallic and ellagic acids; caffeic acid, friedelin and β-sistosterol	*n*-Butanol fraction of *B. micrantha* was the most active with an IC_{50} of 7.3 μg/ml against the RDDP function of HIV-1 RT	Bessong et al. (2006)
Ricinus communis L.	Euphorbiaceae	Essential oils such as α-thujone, 1,8-cineole, α-pinene, camphor and camphene	RDDP IC_{50} = 42.5 μg/ml for a methanol extract	Bessong et al. (2005)
Caesalpinia coriaria (Jacq.) Willd.	Fabaceae	Gallotannin called corilagin has anti-RT activity	IC_{50} = 6.24 μg/ml	Li et al. (2018a,b,c)
Sutherlandia frutescens (L.) R.Br. ex W.T.Aiton	Fabaceae	Free amino acids, non-protein amino acids such as canavanine and GABA, cyclitol pinitol, flavonoids, triterpenoid saponins, hexadecanoic acid, γ-sitosterol, stigmast-4-en-3-one and at least three long chain fatty acids	RNase H IC_{50} = 100 μg/ml for water extract; >50% inhibition	Prinsloo et al. (2018), Van Wyk and Albrecht (2008), Harnett et al. (2005)
Vigna sesquipedalis (L.) Fruwirth	Fabaceae	A polygalactouronic acid-specific lectin (sesquin)	Inhibits RT with IC_{50} of 0.73 μM	Wong and Ng (2005)
Phaseolus vulgaris L.	Fabaceae	*P. vulgaris* lectins block HIV replication by directly inhibiting HIV-1 RT	About 95.4% HIV-1 RT inhibition by 5 mg/ml red kidney bean lectin with an EC_{50} of 2.19 mg/ml	He et al. (2018a,b), Wang and Ng (2001)
Pterocarpus angolensis DC.	Fabaceae	Total phenolics, flavonoids, gallotannin	Leaf meathnol extract, IC_{50} = 0.03 ± 0.00 mg/ml	Mulaudzi et al. (2011)
Peltophorum africanum Sond.	Fabaceae	Flavonoids and C-galloyl glycosides namely (+)-catechin, bergenin and betulinic acid, a naturally occurring pentacyclic triterpene belonging to the lupane family; gallotannin	RDDP IC_{50} = 3.5 μg/ml for a methanol extract; RNase H IC_{50} = 10.6 for methanol extract; gallotannin inhibited the RDDP and RNase H functions of RT with IC_{50} values of 6.0 and 5.0 μM, respectively; catechin and bergenin showed no effect on RT; IC_{50} = 0.05 mg/ml for methanol bark extract	Mulaudzi et al. (2011), Bessong et al. (2005)
Detarium microcarpum Guill. & Perr.	Fabaceae	Catechins; (−)epicatechin 3-gallate being the most potent	IC_{50} = 0.5 μg/ml	Moore and Pizza (1992)
Acacia auriculiformis A.Cunn. ex Benth.	Fabaceae	Alkaloids, ellagic acid, and for saponins	Alkaloids and ellagic acid inhibit RT with IC_{50} = 200 μg/ml; anti-RT activity for saponins, IC_{50} = 0.5 μg/ml	Narayan et al. (2013), Bodeker et al. (2001)
		Unknown compounds in n-butanol fraction		Modi et al. (2013), Silprasit et al. (2011)
Acacia catechu (L.f.) Willd.		A dimeric 70-kDa chymotrypsin inhibits RT; a chitinase-like antifungal protein designated as acaconin isolated from *A. confusa* seeds	Silprasit et al. (2011) found <10% inhibition of RT by hexane extract; Modi et al. (2013) reported that	Lam and Ng (2010)
Acacia confusa Merr. Seeds		inhibited RT; another protein, acafusin inhibits RT mildly	n-butanol fraction had potent inhibitory activity against the viral protease (IC_{50} = 12.9 μg/ml) but not RT	Mamba et al. (2016), Mulaudzi et al. (2011)
Acacia karroo Hayne		25 compounds including epicatechin, β-sitosterol, (−)-epigallocatechin gallate (EGCG), cyclohexanone, 2-methylene-5-(1-methylethyl)	70-kDa chymotrypsin inhibitor, IC_{50} of 8 μM, complete inhibition at 100 μM; chitinase-like antifungal protein, IC_{50} = 10 μM; acafusin, IC_{50} of 80 μM	Rukunga et al. (2002)
Acacia mellifera Benth.			70% RT inhibition at 1 mg/ml; EGCG strongly inhibits RDDP, IC_{50} values as low as 45 nM	
			Stem bark water extract inhibits RT by 85%	

Box 1 (*Continued*)

Species	Family	Phytochemical diversity	Reverse transcriptase inhibitory profiles	References
Psoralea corylifolia L.	Fabaceae	Isobavachalcone, a prenylated chalcone of the class flavonoid	56.26% inhibition of RT at 100 μg/ml	Kuete and Sandjo (2012)
Bolusanthus speciosus Harms	Fabaceae	Total phenolics, flavonoids, gallotannin, and condensed tannin	Leaf methanol extract, IC_{50} = 0.43 mg/ml	Mulaudzi et al. (2011)
Swertia franchetiana Harry Sm.	Gentianaceae	Flavonone-xanthone glucoside, iridoid glycosides, xanthones, xanthone glycosides, flavone glycosides, and triterpenoids; main constituent is swertifrancheside	Swertifrancheside, IC_{50} = 43 μM	Narayan et al. (2013)
Hypoxis sobolifera var. *sobolifera* (Jacq.) Nel	Hypoxidaceae	*Hypoxis* spp. are rich in hypoxoside, β-sitosterol, aglycone rooperol, tannins, sterols and sterolins;	*H. sobolifera* aqueous extract inhibits RT by approx. 80% at 0.2 mg/ml, but this reduces to 10.1% after removal of tannins to 3 and 5% (w/w)	Ncube et al. (2013) Klos et al. (2009)
Hypoxis hemerocallidea Fisch., C.A.Mey. & Avé-Lall.			*H. hemerocallidea* extract, IC_{50} = 17.4 μg/ml; methanol extract of tuber has TI of 15 to 18, and reduction factor of 10^3	
Salvia officinalis L.	Lamiaceae	Oleanolic acid, a pentacyclic triterpenoid	Oleanolic acid, IC_{50} = 1.6–2.0 μg/ml, similar to the authentic oleanolic acid preparation; EC_{50} = 62 μ/ml	Bekut et al. (2018), Watanabe et al. (2000)
Salvia elegans Vahl		The flavonoid apigenin, and 28 volatile constituents, among them are mono- and sesqui-terpenoids such as *trans*-ocimene, linalool, β-caryophyllene, germacrene D and spathulenol, aliphatic alcohols such as 2-propanol and 3-octanol, and trans-3-hexenal	ED_{50} = 3.2 μg/ml, EC_{50} = 31 μg/ml	Bekut et al. (2018), Herrera-Ruiz et al. (2006), Yamasaki et al. (1998)
Leonotis leonurus (L.) R.Br.	Lamiaceae	Tannins, polysaccharides, sterols, diterpenes, triterpenoids, tannins, flavonois, alkaloids, quinines and saponins	Water and ethanol extracts inhibit RT by 60% and 40%, respectively	Klos et al. (2009)
Plectranthus barbatus Andrews	Lamiaceae	Betulinic acid, caffeic acid, diterpenes and forskolin	Extracts have poor inhibition of RT of <50%	Kapewangolo et al. (2013)
Thymus quinquecostatus Čelak.	Lamiaceae	(−)-catechin, chlorogenic acid, rutin, and rosmarinic acid	EC_{50} = 31 μg/ml; weak activity against RT, ED_{50} = 128 μg/ml	Bekut et al. (2018), Hyun et al. (2014), Yamasaki et al. (1998)
Thymus serpyllum L.		*p*-cymene and γ-terpinene; potent activity against RT	ED_{50} = 7.6 μg/ml; EC_{50} = 31 μg/ml	Bekut et al. (2018), D'Auria and Racioppi (2015), Yamasaki et al. (1998)
Mentha spicata L.	Lamiaceae	Phenolics, flavonoids, tannins, gallic acid, quinic acid, caffeic acid, 3,4-di-*O*-caffeoylquinic acid, naringenin, *trans*-ferulic acid, (−)-carvone, limonene, carvacrol and thymol	EC_{50} = 31 μg/ml	Bekut et al. (2018), Ben Saad et al. (2017), Fatiha et al. (2015), Snoussi et al. (2015)
Mentha longifolia (L.) L.			Up to 90% inhibition of RT	Amzazi et al. (2003)
		Flavonoids, phenolic acids, cinnamates, ceramides, sesquiterpenes, terpenes, and terpenoids; flavonoids include apigenin-7-*O*-glucoside, apigenin-7-*O*-rutinoside, apigenin-7-*O*-glucoronide; monoterpenes such as α-pinene, β-pinene, 1,8-cineole, limonene, p-cymene, menthol and ocimene; flavonoids are the major inhibitors of RT		
Melissa officinalis L.	Lamiaceae	Rosmarinic acid	Potent activity against RT, EC_{50} = 16 μg/ml, ED_{50} = 1.6 μg/ml	Bekut et al. (2018), Yamasaki et al. (1998)
Ocimum basilicum L. cultivar "cinnamon"	Lamiaceae	Phenolics such as rosmarinic acid, chicoric and caffeic acids; essential oils such as linalool, α-bergamotene (**2**), epi-α-cadinol;	Potent activity against RT, EC_{50} = 16 μg/ml, ED_{50} = 15 μg/ml	Bekut et al. (2018), Kwee and Niemeyer (2011), Hussain et al. (2008), Yamasaki et al. (1998)
Ocimum labiatum (N.E.Br.) A.J.Paton		Pheophytin-a	Weak inhibition of 21% against HIV-1 RT	Kapewangolo et al. (2017) Sonar et al. (2017)
Ocimum sanctum L.		Betulinic acid, oleanolic acid, ursolic acid, pomolic acid, stigmasterol, vanillin, and ferulaldehyde; five triterpenes and three 3-methoxy-4-hydroxy phenyl derivatives including tetradecyl ferulate; among triterpenes, ursolic acid was the most potent inhibitor; oleanolic acid and pomolic acid show high anti-RT potency	Five triterpenes and three 3-methoxy-4-hydroxy phenyl derivatives including tetradecyl ferulate showed RNase H IC_{50} value of 12.4 μM; dichloromethane leaf extract has good RNase H inhibition, IC_{50} of 4.2 μg/ml; ursolic acid was the most potent inhibitor, IC_{50} = 5.5 μM; oleanolic acid and pomolic acid exert high anti-RT potency, IC_{50} of 7.5 and 9.3 μM, respectively	
Perilla frutescens Britton	Lamiaceae	Polyphenol compounds including anthocyanins and flavonoids	ED_{50} = 7.1 μg/ml	Saita et al. (2012), Yamasaki et al. (1998)
Satureja montana L.	Lamiaceae	Triterpenes, phenolic compounds, and essential oils such as thymol, *p*-cymene, γ-terpinene and carvacrol; aglycones such as thymoquinone, eugenol, *cis*-3-hexene-1-ol and thymol	Potent activity against RT, EC_{50} = 16 μg/ml, ED_{50} = 5.5 μg/ml	Bekut et al. (2018), Ćetković et al. (2007), Mastelić and Jerković (2003), Yamasaki et al. (1998)

Box 1 (*Continued*)

Species	Family	Phytochemical diversity	Reverse transcriptase inhibitory profiles	References
Lavandula dentata L.	Lamiaceae	29 compounds representing 99.87% of the essential oils: 1,8 cineol, sabinene, myrtenal, α-pinene, borneol, linalool, myrtenol and pinocarvone	ED_{50} = 7.6 μg/ml	Imelouane et al. (2009), Yamasaki et al. (1998)
Scutellaria baicalensis Georgi	Lamiaceae	Flavones such as baicalin, wogonoside and their aglycones baicalein (**1**) wogonin are the major bioactive compounds; baicalin has very good anti-HIV-1 activity as NNRTI; 5,6,7-Trihydorxyflavone (baicalein) has four times stronger inhibitory activity on HIV-1 RT than baicalin; baicalin can be deglycosylated to form baicalein in the human body	2 μg/ml baicalein competively inhibits 90% of the activity of RT; Ki value of baicalein for RT = 0.37 μM	Zhao et al. (2016), Ono et al. (1989)
Prunella vulgaris L.	Lamiaceae	Triterpenoids and their saponins, phenolic acids, sterols and associated glycosides, flavonoids, organic acids, volatile oil and saccharides	Water extract inhibits RT activity with ID_{50} of 26.0 μg/ml; also contains betulinic acid, IC_{50} = 8–13 μM; and ursolic acid, IC_{50} = 5.5 μM	Bai et al. (2016), Kim et al. (2014), Collins et al. (1997)
Hoslundia opposita Vahl	Lamiaceae	Euscaphic acid, hoslunddiol, and 5,7-dimethoxy-6-methylflavone	Inhibit RT by 52% at 100 μg/ml	Said (2017)
Lagerstroemia speciosa Pers.	Lythraceae	Rutin, gallic acid and ellagic acid	Gallic acid inhibits RT by ±70% (50 μg/ml); % inhibition was greater than for nevirapine (1 μM)	Nutan et al. (2013)
Marcetia taxifolia Triana	Melastomataceae	Myricetin, myricetin 3-rhamnoside (MR), myricetin 3-(6-rhamnosylgalactoside) (MRG); all compounds inhibit RT activity	IC_{50} of 10.6 μM for MR and 13.8 μM for MRG; myricetin is the most potent, IC_{50} of 7.6 μM and an inhibition greater than 80%	Ortega et al. (2017)
Azadirachta indica A.Juss.	Meliaceae	More than 300 phytochemicals isolated and characterized including triterpenoids, diterpenoids, steroids such as β-sitosterol and stigmasterol terpenoids; non-isoprenoids include flavonoids (quercetin, catechin and nimbaflavanone), coumarins (scopoletin), isocoumarins (margocetin) *etc.*	A 50 μg/ml of stem bark ethanol extract exerts 88% RT inhibition	Patel et al. (2016), Rukunga et al. (2002)
Bersama engleriana Gürke	Melianthaceae	Phenols, flavonoids, tannins, anthraquinones, saponins, terpenoids, abyssinin, bufadienolidess which are cardiac glycosides, sterols and mangiferin (**3**)	Up to 92% RT inhibition; IC_{50} = 9.38 μg/ml; up to 92% RT inhibition; IC_{50} values of 9.38, 11.95 and 18.75 μg/ml for root, leaf and stem bark extracts, respectively	Mbaveng et al. (2011)
Treculia acuminata Baill. *Treculia africana* Decne. ex Trécul *Treculia obovoidea* N.E.Br.	Moraceae	Triterpenes, coumarins, saponins, phenols, and flavonoids	All studied extracts inhibit at various extents the anti-RT activity at 200 μg/ml; the best IC_{50} values, 31.1 μg/ml, 29.5 μg/ml and 21.1 μg/ml were recorded respectively with the extracts of the leaves of *T. obovoidea*, *T. acuminata* and *T. africana*	Kuete et al. (2010)
Morus nigra Thunb.	Moraceae	Gallic acid, quercetin, and linoleic, palmitic, oleic acids and kuwanon-L	Kuwanon-L inhibits RT with an EC_{50} of 1.9 μM, showing no toxic effect at the highest tested concentration (CC_{50} > 20 μM); kuwanon-L, isolated from the black mulberry tree *M. nigra*, has anti-RT activity comparable to antiretroviral drugs	Cary and Peterlin (2018), Martini et al. (2017), Wang et al. (2017), Esposito et al. (2015)
Moringa oleifera Lam.	Moringaceae	Saponins, alkaloids, glycosides, tannins, carbohydrates, flavonoids, resins, rhamnose, glucosinolates, isothiocyanates, two alkaloids moringine and moringinine, vanillin, β-sitosterol, β-sitostenone, 4-hydroxymellin and octacosanoic acid; rich in protein, calcium, iron and vitamin C	Strong HIV-1 RT inhibitors, IC_{50} = 9 μg/ml for water extract, and IC_{50} = 79 μg/ml for 50% methanol extract; about 35% inhibition of RT mainly due to tannins and flavonoids	Ndhlala et al. (2016), Nworu et al. (2013), Silprasit et al. (2011)
Myrothamnus flabellifolia Welw.	Myrothamnaceae	Gallotannins, 3,4,5-tri-*O*-galloylquinic acids; polyphenolic compounds; pinocarveol, pinocarvone, and β-selinene are the most abundant volatiles, along with α-pinene, limonene, and a few other terpenoids;	Non-competitive inhibitor of RT; IC_{50} for 3, 4, 5, tri-O-galloylquinic acid = 34 μM	Brar et al. (2018)
Eucalyptus globulus Labill. *Eucalyptus globoidea* Blakely	Myrtaceae	β-sitosterol, stigmasterol, euscaphic acid, anthocyanins, eucalyptone, betulinic, gallic and ellagic acids, and macrocarpals A–E; essential oil contains 1,8-cineole (45.4%), limonene (17.8%), p-cymene (9.5%), γ-terpinene (8.8%), α-pinene (4.2%) and α-terpineol (3.4%) Globoidnan A	Macrocarpal C inhibits RT, IC_{50} = 5.3 μM IC_{50} = 0.64 μM	Kato et al. (2018), Nishizawa et al. (1992) Singh et al. (2005)
Eugenia hyemalis Cambess.	Myrtaceae	Galloyl arbutins (hyemalosides A–C)	Inhibit HIV-1 RNase H *in vitro* with IC50 values of 1.46, >18, and 1.19 μM, respectively	Bokesch et al. (2008)

Box 1 (*Continued*)

Species	Family	Phytochemical diversity	Reverse transcriptase inhibitory profiles	References
Ximenia caffra Sond.	Olacaceae	*p*-Coumarins, condensed tannins, flavonoids, gallotannins and phenolics	Aqueous and methanol extracts of roots and leaves show good HIV-1 RT inhibition (>70%) at 1 mg/ml; IC_{50} = 0.15 mg/ml for methanol root extract	Mulaudzi et al. (2011)
Petiveria alliacea L.	Phytolaccaceae	Principal bioactive compounds present in the roots are polysulphides, cysteine sulfoxide derivatives and sulfine; flavonoids have also been isolated from the leaves; thiosulfinates, trisulfides and benzylsulfinic acid were observed to be the most active, with the benzyl-containing thiosulfinates exhibiting the strongest activity	Dibenzyl trisulfide, crude methanol and ethyl acetate extracts inhibited HIV-1 RT in infected cells, with EC_{50} concentrations of 5.60 μg/ml, 21.6 μg/ml and 68.0 μg/ml, respectively; tested extracts had IC_{50}/EC_{50} selectivity index values of ≥1.47	Lowe et al. (2015), Blainski et al. (2010), Kim et al. (2006)
Pinus parviflora Siebold & Zucc	Pinaceae	PC6, an extract from cones, has potent immune modulatory activities	54% inhibition of RT	Tamura et al. (1991)
Limonium morisianum Arrigoni	Plumbaginaceae	Myricetin, myricetin 3-*O*-rutinoside, tryptamine, ferulic acid, phloretic acid, (−)-epigallocatechin 3-*O*-gallate and myricetin-3-*O*-(6″-*O*-galloyl)-β-D-galactopyranoside; (−)-epigallocatechin gallate (EGCG)	EGCG strongly inhibits RDDP, IC_{50} values as low as 45 nM; (−)-epigallocatechin 3-*O*-gallate and myricetin-3-*O*-(6″-*O*-galloyl)-β-D-galactopyranoside inhibit RT with values ranging from 0.21 to 10.9 μM; at a concentration of 1 and 2 μg/ml, myricetin completely inhibits the activities of RT with a Ki value of 0.08 μM; ferulic and phloretic acids are not significantly active against RNase H (IC_{50} values >100 μM), and tryptamine is weakly active on RT, IC_{50} value of 94.9 μM.	Sanna et al. (2018a,b), Semwal et al. (2016)
Rheum palmatum L., *Rheum officinale* Baill.	Polygonaceae	Seven phenolic components such as Aloe-emodin, rhein, emodin, chrysophanol, physcion, sennoside A and sennoside B	Sennoside A (RNase H IC_{50} = 1.9 μM; RDDP IC_{50} = 5.3 μM) and Sennoside B (RNase H IC_{50} = 2.1 μM; RDDP IC_{50} = 2.3 μM) were effective on both RT-associated functions; extracts of *R. palmatum* and *R. officinale* potently inhibit RT with IC_{50} values of 0.9 and 0.25 μg/ml, respectively	Esposito et al. (2016)
Ziziphus mucronata Willd.	Rhamnaceae	Tetracyclic triterpenoid saponins and flavonoids in its fruits, anthocyanins in its roots and bark, vitamin C concentration ranges from 70 to 165 mg per 100 g, cyclopeptide alkaloids *e.g.* mucronines F, G and H	RNase H IC_{50} = 75.0 μg/ml for methanol extract; methanol extract stimulates RT activity at 100 μg/ml	Mokgolodi et al. (2011), Bessong et al. (2005)
Crataegus pinnatifida Bunge	Rosaceae	Ursolic acid	IC_{50} = 8 μM	Singh et al. (2005)
Prunus africana (Hook.f.) Kalkman	Rosaceae	Ferulic acid, n-docosanol, lauric acid myristic acid, β-sitostenone and β-sitosterol	50 μg/ml stem bark methanol extract inhibits RT by 97%	Kadu et al. (2012), Rukunga et al. (2002)
Canthium coromandelicum (Burm.f.) Alston	Rubiaceae	Alkaloids, flavonoids, tannins and polyphenols	Methanolic extract inhibits RT by 78.67%; most studies consider inhibition of ≥50% as significant	Chinnaiyan et al. (2013)
Gardenia carinata Wall.	Rubiaceae	Flavones; cycloartane triterpenoids named carinatins A–H, and the known compounds secaubryolide and dikamaliartane D were isolated from leaves and twigs	Flavonoids have IC50 = 18 to 65 μg/ml on RT; ring-secocycloartene triterpenoids inhibit RT, IC_{50} = 72–94.1 μg/ml; cycloartane compounds (4 mg/ml) inhibit RT by 72–94%, IC_{50} = 1.9–4.2 μM	Kongkum et al. (2013), Akihisa et al. (2001)
Psychotria ipecacuanha Stokes	Rubiaceae	Emetine, an alkaloid	At 0.01 mM of emetine, the reduction in RT activity *in vitro* was up to 50%; complete elimination of RT activity at 0.9 mM of emetine; 90% inhibition of RT activity at 14.4 mM of emetine in cell-free virions; Tan et al. (1991) reported that emetine inhibits 10%–20% of RT activity *in vitro* at 400 μg/ml (0.72 μM)	Valadão et al. (2015), Tan et al. (1991)
Toddalia asiatica Baill.	Rutaceae	Nitidine, an alkaloid	IC_{50} = 14 μM	Yadav et al. (2017), Singh et al. (2005), Rashid et al. (1995)
Nephelium lappaceum L.	Sapindaceae	Lectins; 22.5 kDa protein	Protein exhibits significant HIV-1-RT inhibitory activity with an IC_{50} of 0.73 μM; mechanism of the inhibitory action of protein on RT activity probably involves protein–protein interaction	Fang and Ng (2015)

Box 1 (*Continued*)

Species	Family	Phytochemical diversity	Reverse transcriptase inhibitory profiles	References
Schisandra sphaerandra Stapf	Schisandraceae	Nigranoic acid inhibits RT	IC_{50} = 74.1 μg/ml	Cassels and Asencio (2011), Sun et al. (1996)
Schisandra chinensis (Turcz.) K.Koch		Lignans; among the fruit lignans, schisandrin B and deoxyschisandrin selectively inhibit RT associated DNA polymerase activity; schisandrin B was also able to impair HIV-1 RT drug resistant mutants	EC_{50} values in the 1–3 μM range; one fraction inhibited RT activity in a dose-dependent manner with an IC_{50} of 17.25 μM	Xu et al. (2015) Han et al. (2015)
Schisandra neglecta A.C.Sm.		A dibenzocyclooctadiene lignin		
Solanum xanthocarpum Schrad.	Solanaceae	Flavonoids	Anti-RT activity is low, < 30% for organic and water extracts	Kumar and Pandey (2014)
Daphne acutiloba Rehder	Thymelaeaceae	Phenols, diterpenoids, diterpene esters, sesquiterpenoids, lignans, bioflavonoids, coumarins and flavans; wikstroelide M (a daphnane diterpene)	Wikstroelide M exerts moderate inhibitory effect on RT, EC_{50} = 92.23 ng ml^{-1}, this suggests that wikstroelide M may be a non-specific RT inhibitor	Zhang et al. (2014a,b)
Curcuma longa L.	Zingiberaceae	Curcuminoids including curcumin I, curcumin II, curcumin III and cyclocurcumin; curcumin (diferuloylmethane, from turmeric, the roots/rhizomes of *C. longa*) inhibit RT	Docking results at cavity 1 of RT revealed binding affinity of −11.22; ligand efficiency values of −5.36, −0.41 and −4.10 were observed	Mathew and Hsu (2018), Seal et al. (2011)

medicinal plant resources. More concerted research efforts on the search for drugs from putative anti-HIV-1 RT plants are urgently required in Africa. Indigenous knowledge of plants used as putative herbal drugs for HIV-1 infection is a good starting point in the development of new plant-based HIV-1 RT drugs.

Filter out pan-assay interference compounds

Although plant products represent an enormous source of pharmacologically useful compounds and are often used as the starting point in modern drug discovery, many biologically interesting plant compounds are not being pursued as potential drug candidates because they lack well-defined modes of action (Li et al., 2015). For example, it is unlikely that pheophytin-a (Kapewangolo et al., 2017), a degradation product of chlorophyll which represents chlorophyll that has lost the central Mg^{2+} ion, would be developed into an anti-HIV-1 RT drug. Similarly, the anti-RT therapeutic application of andrographolide is limited because this bioactive bicyclic diterpenoid is a highly promiscuous compound that interacts with numerous and unknown cellular targets; hence it is not seriously considered as a potential drug candidate (Li et al., 2015). In general, the development of novel anti-RT drugs from plants is an uphill task because the classical drug discovery route is long (takes about 12–15 years) and the expenditure is high; around US$ 1 billion (Farooq et al., 2016). In particular, *in vivo* testing and ultimately human clinical trials need to be carried out on key lead plant compounds. Continuous evaluation of anti-HIV-1 RT compounds should also be rigorously pursued because pharmaceutical companies do not progress anti-HIV-1 RT screening hits that are photoreactive, for example 2-aminothiazoles (Baell and Holloway, 2010).

Sink et al. (2010) caution that although high-throughput screening (HTS) is one of the most powerful approaches available for identifying new plant lead compounds (just as virtual and experimental HTS have accelerated lead identification and changed drug discovery), it has also introduced a large number of pan-assay interference compounds (PAINS) which turn out to be dead-ends after a great deal of time and resources have been spent (Sink et al., 2010; Baell and Nissink, 2017). PAINS are frequent hitters (promiscuous compounds) that render efforts to develop novel HIV-1 RT drugs from plant-derived compounds fruitless. They represent poor choices for drug development and can furnish misleading data that in isolation may be suggestive of a selective and optimizable anti-HIV RT hit. Compounds are regarded as false positives if they interfere in binding interactions by forming aggregates, those that are protein-reactive, sometimes light induced, or those that directly interfere in assay signalling (Baell and Holloway, 2010). Putative PAINS include azo compounds, cyanopyridones, divinylketones, certain indoles, quinones, rhodanines and other compounds of cyclic and heterocyclic nature (Baell and Holloway, 2010). PAINS have contributed to the rapidly growing body of anti-HIV-1 RT literature, yet very few screening hits have progressed to the level of candidate drugs (Baell and Holloway, 2010).

Although it is beyond the scope of this review to categorically state which anti-HIV-1 RT phytochemicals are PAINS, active compounds in this review should be screened to ascertain whether they are false positive hits which may present challenges in anti-HIV-1 RT drug development. Suffice to state many studies have been devoted to understanding the origins of PAINS and the findings have been incorporated in filters and methods that can predict and eliminate problematic molecules from further consideration. There are electronic filters which recognize and exclude PAINS from further analysis (Baell and Nissink, 2017). While many PAINS are usually highly promiscuous compounds, others may be important compounds which may be further explored for polypharmacology in general and multi-target anti-HIV-1 RT activities in particular (Gilberg et al., 2016). Stated differently, the practice of excluding PAINS may be fraught with danger because such black box segregation, based entirely on inputs and outputs, without knowledge of internal workings, is as simplistic as it lacks drug-like complexity (Baell and Nissink, 2017). Still, screening for PAINS can help avoid undertaking wasteful studies such as full efficacy, pharmacokinetics, tissue distribution, and metabolism experiments destined for failure (Baell and Holloway, 2010).

Analysis of structure–activity relationships

Structural modification of plant-derived active principles may provide a continuous source of potential anti-HIV-1 RT drug candidates. Certain structural features of plant products are responsible for their anti-HIV-1 RT biological activities. Identifying such special scaffolds is of great importance because laboratory synthesis of molecules containing similar scaffolds can serve as an effective strategy for new drug synthesis (Zhao et al., 2018a,b). Already, a pharmaceutical formulation which consists of an arylnaphthalene lignan compound, based on justiprocumin A isolated from the plant *J. gendarussa*, Acanthaceae, has been patented as an effective treatment for HIV/AIDS (Zhang et al., 2014a,b). In structure–activity relationship studies, patentiflorin A, a novel arylnaphthalene

lignan from *J. gendarussa* plants in Vietnam, showed potential as an anti-HIV-1 RT drug. Patentiflorin A was more effective than AZT in inhibiting four different HIV-1 isolates, IC_{50} values in the range 14–32 nM (Zhao et al., 2018a,b).

Phenylethylthiazolylthiourea (PETT) derivatives have been identified as a new series of non-nucleoside inhibitors of HIV-1 RT (Cantrell et al., 1996). Structure–activity relationship studies of this class of compounds resulted in the identification of *N*-[2-(2-pyridyl)ethyl]-*N*′-[2-(5-bromopyridyl)]thiourea hydrochloride (trovirdine; LY300046·HCl) as a highly potent anti-HIV-1 RT agent (Cantrell et al., 1996). Trovirdine is currently in phase one clinical trials for potential use in the treatment of AIDS. Comparative studies with flavonoids (hydroxyflavones, dihydroxyflavones and polyhydroxyflavones and flavanones), carried out to clarify the structure–activity relationships, revealed that the presence of both the unsaturated double bond between positions 2 and 3 of the flavonoid pyrone ring, and the three hydroxyl groups introduced on positions 5, 6 and 7 were a prerequisite for the inhibition of HIV-1 RT activity (Ono et al., 1990).

Analysis of structure–activity relationships has been helpful in understanding the mechanisms of quercetagetin which contains the structures of both baicalein (**1**) and quercetin, and myricetin which has the structure of quercetin with an additional hydroxyl group on the 5′ position. Quercetagetin and myricetin are strong inhibitors of HIV-1 RT activity (Ono et al., 1990). The RT inhibition by baicalein is highly specific whereas quercetin and quercetagetin are also strong inhibitors of DNA polymerase β and DNA polymerase I, respectively. Myricetin is a potent inhibitor of both DNA polymerase α and DNA polymerase I (Ono et al., 1990). While the anti-RT activity of the alkaloid castanospermine was high, IC_{50} 1.1 μM (Whitby et al., 2004), several of its *O*-acyl derivatives are 20 times more active than AZT. However, *O*-acyl derivatives were highly toxic and unsuitable for further development into anti-HIV drugs (Hamburger and Hostettmann, 1991). Advances in synthetic chemistry can also generate derivatives with improved efficacies that are orders of magnitude greater than the parent plant product-derived compounds. A mono-methyl substitution enhanced the potency of coumarin analogues. A 4-methyl substituted lactam derivative had potent anti-RT activity in acutely infected H9 lymphocytes and was about 225-fold more active than AZT in the same assay (Yu et al., 2003).

Further studies including *in silico* molecular docking simulations and X-ray diffraction should be done to investigate the binding affinities of plant active compounds to HIV-1 RT. Future studies should also focus on the elaboration of new derivatives with better anti-RT activities than original plant-derived active ingredients. The discovery of potent anti-RT plant-derived compounds can also be enhanced by computational and virtual screening of compound library databases. In this approach, electronic compound libraries are probed for a series of chemical pharmacophores shared by compounds known to exhibit a known pharmacological property (Andersen et al., 2018). The performance of computer algorithms in generating reliable 3D conformers of compound models and the speed of docking algorithms have improved tremendously over the past decade, thus making these approaches accessible even to small, remote, or resource-limited laboratories (Andersen et al., 2018). Several computer programmes that utilize statistically-derived structure–toxicity/metabolism relationships have been developed for the prediction of toxicity and metabolism, so as to combat the main drawbacks (time and financial costs) in traditional drug discovery methods as well as to promote animal welfare (Onguéné et al., 2018).

Barreca et al. (2002) performed the design, synthesis, and the structure–activity relationship studies of a series of 2,3-diaryl-1, 3-thiazolidin-4-ones and found that some derivatives were highly effective in inhibiting HIV-1 RT at nanomolar concentrations with minimal cytotoxicity. Thus, computational studies can be used to delineate the ligand-RT interactions and to probe the binding of the ligands to HIV-1 RT (Barreca et al., 2002). Hannongbua et al. (2001) applied comparative molecular field analysis (CoMFA) to a large set of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) analogues. The starting geometry of HEPT was obtained from crystallographic data of HEPT/HIV-1 RT complexes. The structures of 101 HEPT derivatives were considered and fully optimized by *ab initio* molecular orbital calculations at the HF/3-21G level. Hannongbua et al. (2001) found that the best CoMFA model was satisfactory in both statistical significance and predictive ability of 0.858. Their derived model showed the importance of steric contributions (64.4%) and electrostatic interactions for HIV-1 RT inhibition.

In addition, steric and electrostatic contour maps from their analysis were in conformity with the experimentally observed trend that there were steric interactions between the side chain of HEPT and an aromatic ring of Tyr181 (Hannongbua et al., 2001). A moderately sized group at C5 enhances contact with Tyr181 enough to push it into a position which renders the protein non-functional, but a smaller group has insufficient steric requirements to do this and a larger group renders the ligand too large for the cavity. These results not only help to explain the mutation-induced resistance of HIV-1 RT but also lead to a better understanding of structural requirements of HEPT analogues for the inhibition RT. This is important for the design of novel and more potent anti-RT drugs.

Application of structure-based drug design strategies may aid in the development of novel HIV-1 RT inhibitors (Ding et al., 2018). Detailed analysis of the conformational changes among the various HIV-1 RT structures is important. It may reveal additional sites for binding new plant-derived inhibitors or show sites where plant agents can interfere with the polymerization and/or flexibility of the RT enzyme. The considerable physical and genetic flexibility of HIV-1 RT also suggests that more effective anti-RT drugs should be designed to target the conserved portions of HIV-1 RT that the virus cannot easily afford to change. Therefore, an important issue in analyzing the structure–activity relationship of HIV is the genetic flexibility of the RT enzyme, and this makes the development of novel plant-derived RT inhibitors a difficult task (Ding et al., 2018).

Binding affinity is a measure of the tightness with which an active plant compound attaches to HIV-1 RT. Besides efficacy, binding is one of the factors that influences potency (Uzochukwu et al., 2016). The pleiotropic ability of plant active compounds to bind concurrently to more than one target may be a great advantage because of the expected synergistic effect of such multi-target inhibitors (Uzochukwu et al., 2016). Thus, a possible drug-design strategy would be to devise compounds that can interfere with the binding of the metal ions (Mg^{2+} or Mn^{2+}) at the polymerase active site (Ding et al., 2018). It is also attractive to consider developing agents that bind to HIV-1 RT polymerase active site but are not nucleoside analogues (Ding et al., 2018).

As new knowledge on mechanisms of polymerization, drug inhibition and drug resistance is emerging from studies on structure–function relationships, it may be possible to develop new or improved plant-derived HIV-1 RT inhibitors that may circumvent current patterns of drug resistance mutations (Ding et al., 2018). On the other hand, binding alone does not determine the overall potency phytochemical compounds because it does not always correlate with inactivation of HIV-1 RT (Uzochukwu et al., 2016).

More clinical trials are urgently needed

In terms of drug development, there has been chequered progress with plant-derived anti-HIV-1 RT compounds. For example, some coumarins from plants and their analogues have unique mechanisms of action against HIV-1 replication and

can serve as potent RT inhibitors (Kostova, 2006). Yu et al. (2003) discovered a dicamphanoyl-khellactone (DCK) analogue, a 3-hydroxymethyl-4-methyl khellactone coumarin derivative, a modified form of suksdorfin isolated from methanol extracts of the plant *Lomatium suksdorfii* (Saklani and Kutty, 2008). DCK (PA-334B) is a nanomolar inhibitor of drug resistant HIV-1 isolates. Panacos pharmaceutical completed the required DCK preclinical studies for IND filing (Saklani and Kutty, 2008), but there is no information whether DCK has been taken to clinical trial.

Based on *in vitro* and *in vivo* studies, calanolides are attractive candidates for therapeutic use because they do not have antagonistic anti-HIV-1 drug interactions or synergistic toxicity, in addition to being active against other infectious agents (Yu et al., 2003). Calanolide A proceeded into preclinical and clinical trials (Yu et al., 2003). It also has activity against all *Mycobacterium tuberculosis* strains thus may allow more efficient treatment of patients co-infected with HIV and tuberculosis (Saklani and Kutty, 2008). Synergy of calanolides with AZT was also confirmed *in vivo* along with its significant anti-HIV-1 RT activity (Yu et al., 2003). According to Yu et al. (2003), phase IA studies showed that calanolide A was generally well tolerated in doses up to 600 mg. In human subjects, plasma levels of calanolide A were higher than those predicted from animal studies.

In phase IB studies, calanolide A was administered orally to HIV infected subjects. Clinical and laboratory assessment on viral load and CD4 count indicated that anti-HIV-1 effects of calanolide A appeared to be dose-dependent and maximized on day 14 or 16 (Yu et al., 2003). Calanolide A was also in phase II clinical trials (Saklani and Kutty, 2008). Sarawak Medichem Pharmaceuticals screened volunteers for combination therapy of calanolide A for treating HIV/AIDS, and hoped to progress to phase III clinical trials in late 2002. However, its development was on hold and its fate was dependent on the Sarawak government who owned Sarwak Medichem Pharmaceuticals and its HIV therapeutic candidates (Saklani and Kutty, 2008). Excellent results in preclinical studies and early clinical trials with calanolides demonstrate that coumarin compounds have significant activity and unique HIV inhibitory mechanisms with potential for future drug development and therapy.

In phase I trials was 3,5-di-*O*-caffeoylquinic acid, isolated from the plant *Inula britannica* (Saklani and Kutty, 2008). China's Academy of Military Sciences carried out clinical trials for the compound which acts as an irreversible inhibitor of HIV-1 RT (Saklani and Kutty, 2008). QS-21 based on saponins derived from the South American tree *Quillaja saponaria*, Rosaceae, was an integral part of experimental vaccines evaluated in phase II and III trials for HIV and other infectious diseases (Saklani and Kutty, 2008). Crofelemer (CAS 148465-45-6) was in phase III trials (Saklani and Kutty, 2008). It is an oligomeric proanthocyanidin developed by Napo's partners, Trine Pharmaceuticals Inc. and AsiaPharm Group Ltd. Derived from the latex of *Croton lecheri*, Euphorbiaceae, to treat different types of HIV-induced diarrhoea, Crofelemer was in various stages of clinical development for four distinct product indications including CRO-HIV for AIDS diarrhoea in Phase III (Saklani and Kutty, 2008). Napo obtained Special Protocol Assessment (SPA) agreement from U.S. FDA for Crofelemer in HIV/AIDS Diarrhoea Assessment (Saklani and Kutty, 2008).

An anti-RT inhibitor from plants mentioned in this review, betulinic acid is usually found as free aglycon or as glycosyl derivatives. Some betulinic acid derivatives such as Bevirimat (lacking the carboxyl C-28) have higher anti-HIV-1 potency than the parent compound (Ríos and Máñez, 2018). PA-457 (Bevirimat) was in phase IIb trials (Saklani and Kutty, 2008). Panacos Pharmaceutical developed PA-457 as an anti-HIV drug (maturation inhibitor). The antiretroviral activity of PA-457 is pleiotropic as it also blocks a late step in the processing of HIV group-specific antigen (Gag) protein (Saklani and Kutty, 2008). The resulting HIV particles are structurally defective and incapable of spreading infection in the body (Saklani and Kutty, 2008). Due to its poor solubility in water, betulinic acid has low gastrointestinal absorption which never exceeds 1% (Ríos and Máñez, 2018). Therefore, the main limitation to the clinical use of betulinic acid is its poor hydrosolubility. For HIV therapy, further studies are needed to develop novel administration formulations and methods for betulinic acid.

Isolation of pure compounds and the poor water-solubility of active plant-derived RT inhibitors and their active analogues can limit their further development as drug candidates (Yu et al., 2003). Therefore, introducing polar functional groups into the structure may improve water solubility and provide the possibility of prodrugs (Yu et al., 2003). Notwithstanding, derivatives of betulinic acid are promising compounds for treating HIV/AIDS (Ríos and Máñez, 2018). Succinyl and 3′-substituted glutaryl betulin derivatives show stronger anti-HIV activity and higher therapeutic index values than their dihydrobetulin counterparts (Sun et al., 1998). Due to its pleiotropic biological effects, especially its outstanding anti-HIV RT activity, betulinic acid isolated from various medicinal plants continues to attract the attention of many scientists (Huang et al., 2018). By June 2018, some derivatives of betulinic acid with inhibitory activities at nanomolar concentrations had entered phase II clinical trials (Huang et al., 2018).

Celgosivir synthesized by selective *C*-acylation of castanospermine is rapidly converted to castanospermine *in vivo* (Sung et al., 2016). Celgosivir is a 6-*O*-butanoyl prodrug of castanospermine (Low et al., 2014). Combination therapy of 6-*O*-butanoyl castanospermine (Celgosivir) with Peginterferon and/or Ribavirin was tested in phase II clinical trials for the treatment of patients with chronic hepatitis C virus (Wojtowicz et al., 2016). Although generally safe and well tolerated, Celgosivir did not reduce viral loads (Sung et al., 2016). After tests in phase 1 and 2 trials as a possible treatment for HIV infection, Celgosivir's efficacy was not superior to existing treatments; hence testing was discontinued (Low et al., 2014).

A large number of peptides such as ascalin interrupt HIV-1 replication. Natural and synthetic peptides are being studied for their possible clinical applications in preventing HIV-1 infection due to their low systemic toxicity; this is their main advantage (Ng et al., 2015). Although lupeol binds to an HIV-1 RT allosteric pocket (Esposito et al., 2017) and has high bioavailability, factors such as effective dose and the duration of treatment limit its therapeutic applications (Siddique and Saleem, 2011). Clinical trials with lignans also produced disappointing outcomes (Hamburger and Hostettmann, 1991).

Only 1 in 250,000 plant samples may directly lead to a commercial drug (Macilwain, 1998). Unsurprisingly, there are few plant-derived anti-HIV-1 RT agents in clinical trials. In fact, there were no plant-based HIV/AIDS drugs approved or launched during the period of 2000–2006 (Saklani and Kutty, 2008). In 2008, plant-derived compounds which were in clinical trials were 3,5-di-*O*-caffeoylquinic acid, calanolide A, castanospermine, and betulinic acid (Saklani and Kutty, 2008). From 2012 to 2017, only twelve new antivirals were approved by the FDA in the USA; eight are for the treatment of pathologies related to hepatitis C virus and two are combinations of anti-HIV drugs (Mercorelli et al., 2018). There are few scientific reports on plant compounds in clinical trials for the treatment of HIV/AIDS because this field is not well researched (Salehi et al., 2018). Further, most of the studies are *in vitro* and very few investigations have been performed *in vivo* or in humans (Salehi et al., 2018). Since only 10–15% of plant diversity is explored for pharmaceutical purposes (Saklani and Kutty, 2008), the transition from natural product to anti-HIV-1 RT drug prototypes is a daunting prospect.

Limitations in current research on HIV-1 RT inihibitors from plants

The main weakness is that majority of the studies are based on *in vitro* models and merely report broad phytochemical groups such as phenolic acids, flavonoids and terpenes as being the active molecules against HIV-1 RT. Therefore, there is an urgent need to pinpoint exact novel plant chemical compounds that inhibit HIV-1 RT. The lack of clinical data to support the reported *in vitro* biological activity is also a major shortcoming. This makes it difficult to depict any novel plant compounds with real promise for clinical application. Anti-HIV-1 RT plant extracts and active compounds should be rigorously tested in animal and human trials. But at the moment there is a paucity of clinical data. Clinical research data may provide more concrete information on the efficacy of medicinal plants as potent inhibitors of HIV-1 RT. Although many plants possess anti-HIV-1 RT properties, their extracts and active compounds should be evaluated for human cytotoxicity and dosage. Further studies on pharmacovigilance and interactions between synthetic cART drugs and plant chemical compounds are also needed.

While crude extracts and some isolated compounds are active against HIV-1 RT, others are toxic to human cells. Such toxic plant compounds should be redirected into different pipelines including the possibilities to be used anticancer agents. Toxic compounds should also be modified through the use of computational chemistry. More data on the structure–activity relationships for plant active compounds and their derivatives are still needed. Screening for anti-HIV-1 RT activity is commendable but current approaches are cul-de-sac scientific expeditions because they have not yielded patentable molecules and commercial products or clinical drugs. Many compounds described in this review reportedly display off-target activity and/or are vulnerable to facile excretion upon metabolism, thereby limiting their appeal as clinically useful HIV-1 RT inhibitors. This challenge could be addressed by the relevant experiments on absorption–distribution–metabolism–excretion (ADME). There is also need for more data on the chemical stability of the active compounds and their susceptibility to oxygen, light and aqueous environment.

Conclusion

This review provides an insightful snapshot of species, genera and families of plants that contain chemical compounds that work as inhibitors of HIV-1 RT. Chemical diversity and anti-HIV-1 RT inhibitory profiles of the various plants have been presented. Anti-RT inhibitors from plants have a plurality of functions. Many of the active compounds against HIV-1 RT are promiscuous with known pleiotropic pharmacological effects. The multiplicity of pharmacological effects was initially heralded as being advantageous but it seems to have become the lightning rod that has drawn to it the negative impulses not least the lack of commercial interest to develop the active compounds into new antiretroviral drugs. Therefore, despite current optimism emanating from their reported anti-RT activities, the phytochemicals have limited high-end clinical applications. Their therapeutic potential is still a distant goal as the molecules are still at the screening stage and initial phases of the drug discovery pipeline. The manufacture of anti-HIV herbal medicines may be a viable option in resource-poor settings. Current anti-HIV-1 RT inhibitors from plants can be repurposed to treat other diseases. To accelerate drug discovery and development, there is an urgent need to tap into the rich vein of indigenous knowledge of putative anti-HIV/AIDS medicinal plants (reverse pharmacology), determine pan-assay interference compounds, analyze structure–activity relationships, and conduct more clinical trials.

Conflicts of interest

The author declares no conflicts of interest.

Acknowledgements

Moola Nyambe is thanked for drawing the chemical sctructures. Editors and anonymous reviewers are thanked for their comments which improved the original manuscript.

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