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REVIEW PAPER

Anti-HIV activity of some natural phenolics

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Summary

Acquired immunodeficiency syndrome (AIDS) is an immunosuppressive disease caused by human immunodeficiency virus (HIV). The urgent need for searching novel anti-HIV/AIDS medicines is a global concern. So far, a lot of medicinal and aromatic plants (MAPs) have been analyzed to select those that could assist in the prevention and/or amelioration of the disease. Among biologically active compounds present in these plants, one of the most promising group are phenolics. The purpose of this article was to report anti-HIV activity of selected phenolic compounds of plant origin.

Keywords: ***medicinal plants, phenolics, AIDS, anti-HIV activity, mechanism of action***

Słowa kluczowe: ***rośliny lecznicze, związki fenolowe, AIDS, działanie anty-HIV, mechanizm działania***

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV) is an immuno-suppressive disease resulting in life-threatening infections and malignancies. According to World Health Organization (WHO), about 75 million people suffer from HIV. It has become the main reason of death in Africa and South-east Asia [1]. The risk of infection increases significantly due to the limited access to education, non-hygienic lifestyle, and unsafe sexual behaviours. Usually, after the infection, natural defense system of an individual is severely disturbed. Currently, there are no efficacious methods of total destruction of the virus, however, the discovery of anti-retroviral agents has decreased it's mortality. During therapy, viral replication is highly restricted, however, the therapy involves dangerous side effects. Another problem is the emergence of viral resistance to anti-HIV agents. Thus, according to WHO recommendations, new natural products should be systematically investigated to select substances of potential anti-HIV effects. The biodiversity of plant kingdom

has provided a wide source of biologically active compounds for such research. The number of compounds isolated of plant origin, exhibiting anti-HIV activity, is increasing steadily. Among them, phenolics seem to be one of the most numerous, diverse and promising [2-4].

PLANT PHENOLICS WITH ANTI-HIV ACTIVITY

Phenolics are a group of secondary metabolites produced on the phenylpropanoid pathway. Their structure is based on a benzene ring, with one or more hydroxyl groups attached. In the plant kingdom, these are one of the most diverse and most dispersed compounds. From simple compounds to complex polyphenols, they play an important function in plants development and plant-environment interactions [2]. In recent years, the role of phenolics in the prevention and treatment of many disease has been investigated [3]. So far, anti-HIV activity of these compounds has been reported using both *in vitro* and *in vivo* model of the investigations.

Flavonoids

The general structure of flavonoids is based on a 15-carbon skeleton consisting of two phenyl rings (A and B) and one heterocyclic ring (C). In plants, they occur in a free or conjugated form, often as glycosides with sugar moieties linked through OH group (*O*-glycosides) or carbon-carbon bond (*C*-glycosides). Within flavonoids, the following compounds were analysed regarding anti-HIV activity:
- prenylated flavonoids, namely: 6,8-diprenylaromadendrin (fig. 1, compound 1) and 6,8-diprenylkaempferol (fig. 1, compound 2), isolated from *Monotes africanus* A. DC. The compounds showed HIV inhibitory effects in the XTT-based, whole cell screen test [5,6];
- quercetin 3-O-(2'-galloyl)-α -L-arabinopyranoside (fig. 1, compound 3) isolated from *Acer okamotoanum* Nakai, exhibited anti-HIV-1 integrase activity [7];
- biflavonoids (dimeric flavonoids), namely: robustaflavone (C3'-C6" linkage flavonol) (fig. 1, compound 4) and hinokiflavone (C4'-O-C6" linked flavonol) (fig. 1, compound 5) isolated from *Rhus succedanea* (L.) Kuntze., demonstrated activity against HIV-1 reverse transcriptase (RTase) in *in vitro* tests [8];
- wikstrol B (fig. 1, compound 6), biflavonoid obtained from *Wikstroemia indica* (L.) C.A. Mey, showed potent activity against HIV-1 in *in vitro* study, as well [9];
- xanthohumol (fig. 1, compound 7), a prenylchalcone extracted from *Humulus lupulus* L., inhibited HIV-1 induced cytopathic effects, the production of viral p24 antigen and reverse transcriptase in C8166 lymphocytes at non-cytotoxic concentrations [10];
- swertifrancheside, a flavone-xanthone glucoside (fig. 1, compound 8) isolated from *Swertia franchetiana* Harry Sm. revealed inhibitory activity against HIV-1 RTase. The mode of action was related to its binding with DNA [11];
- lawinal (fig. 1, compound 9) isolated from genus *Desmos*, showed strong anti-HIV activity (EC50 of 0.022 μg/ml) and high therapeutic indexes [12];
- acacetin-7-O-β-D-galactopyranoside, an active anti-HIV compound (fig. 1, compound 10) has been isolated from *Chrysanthemum morifolium* Ramat. along with chrysin (fig. 1, compound 11) and 7-O-β-D-(4'-caffeoyl)glucuronyl apigenin (fig. 1, compound 15), of similar activity [13, 14];
- baicalin (fig. 1, compound 12) isolated from *Scutellaria baicalensis* Georgi. showed the inhibition of HIV-1 replication in peripheral blood mononuclear cell (PBMC) in a dose dependent manner (IC_{50} values of 0.2 – 0.5 μg/ml) [15, 16];
- taxifolin, also called dihydroquercetin (fig. 1, compound 13), isolated from *Juglans mandshurica* Maxim., exhibited strong inhibition of HIV-induced cytopathic activity against MT-4 cells with complete inhibitory concentration (IC100) value of 25 μg/ml and a maximum cytotoxic concentration (CC100) at 100 μg/ml [17];
- (-)epigallocatechin gallate (fig. 1, compound 14) from green tea leaf (*Camellia sinensis* (L.) Kuntze), showed potent inhibitory activity against enzyme HIV-1 RTase (IC_{50} of 0.01 μg/ml) [18];
- due to the viral protease inhibition the maturation of infectious progeny virus was reduced by kaempferol (fig. 1, compound 16) isolated from *Rosa damascena* Herrm. Quercetin (fig. 1, compound 17) extracted from this plant prevented binding of gp120 to CD4 [19].

Lignans

Lignans are phenolic compounds derived from phenylalanine through dimerization of cinnamic alcohols to dibenzylbutane. Their structure is based on

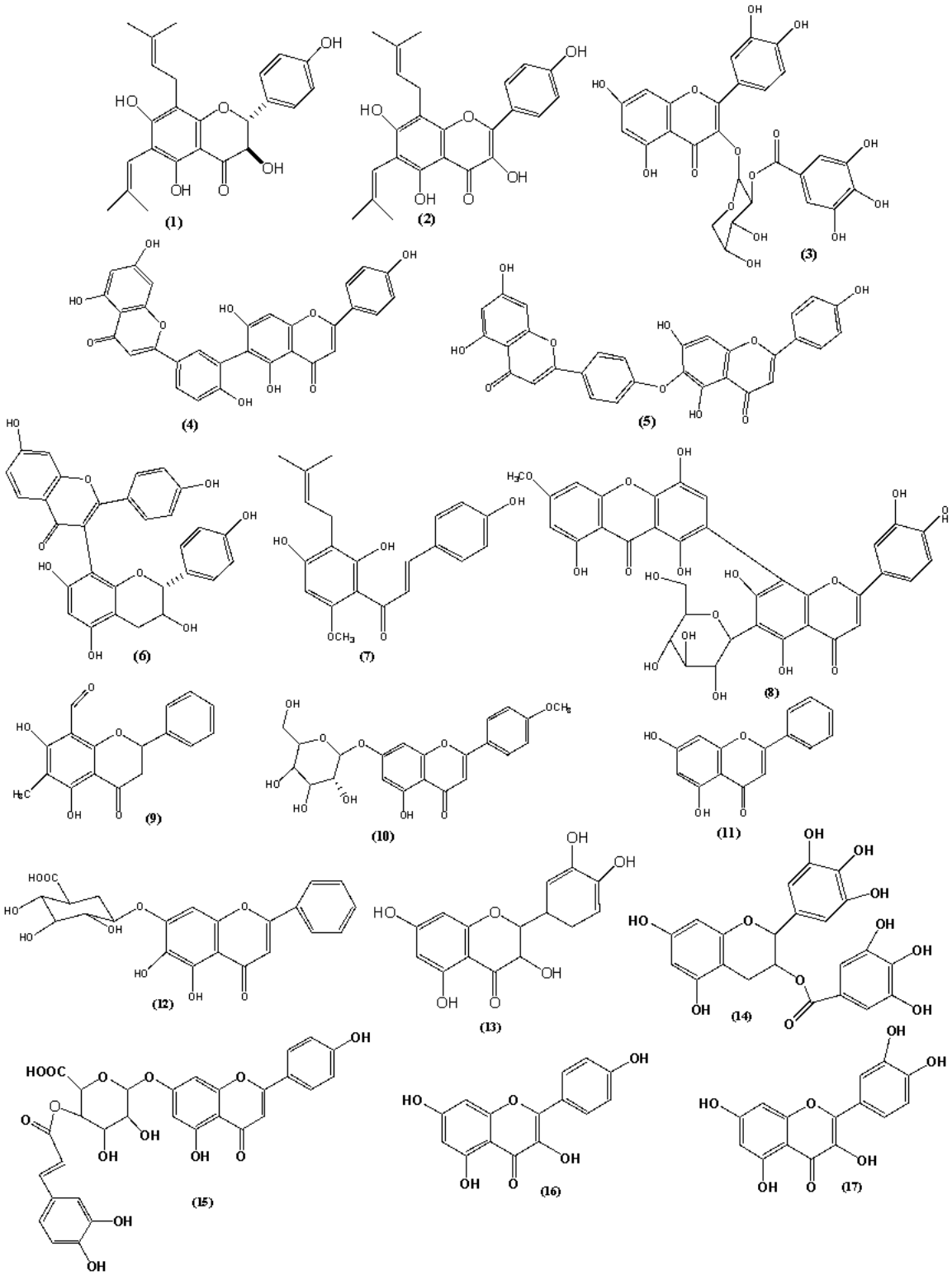

Figure 1

The chemical structures of flavonoids with anti-HIV activity: (1) 6,8-diprenylaromadendrin, (2) 6,8-diprenylkaempferol, (3) quercetin 3-O-(2'-galloyl)-α-L-arabinopyranoside, (4) robustaflavone, (5) hinokiflavone, (6) wikstrol B, (7) xanthohumol, (8) swertifrancheside, (9) lawinal, (10) acacetin-7-O-*β*-D-galactopyranoside, (11) chrysin, (12) baicalin, (13) taxifolin, (14) (-)epigallocatechin gallate, (15) 7-O-*β*-D-(4'-caffeoyl)glucuronyl apigenin, (16) kaempferol, (17) quercetin

two phenylpropanoid skeletons. Some of them, i.e. podophyllin (*Podophyllum peltatum* L.) reveal anticancer activity. Others have been analyzed in terms of anti-HIV activity, e.g:
- *Anogeissus acuminate* (Roxb. ex DC.) Wall. ex Guillen & Perr. is a source of anolignan A (fig. 2, compound 18) and B (fig. 2, compound 19). These compounds showed inhibitory activity against HIV-1 RTase. They are acting by synergistic effect [20, 21];
- dibenzylbutyrolactone-type lignanolide, (-)-arctigenin (fig. 2, compound 20) isolated from *Ipomoea cairica* (L.) Sweet, exhibited anti-HIV activity due to HIV proviral DNA inhibition [22];
- globoidnan A (fig. 2, compound 21) isolated from *Eucalyptus globoidea* Blakely, was responsible for the inhibition of HIV integrase [23].

Phenolic acids, salts and phenolic aldehyde

This wide group represent a number of compounds revealing anti-HIV activity, including:
- repandusinic acid (fig. 3, compound 22) isolated from *Phyllanthus niruri* L. showed inhibitory activity against HIV-RTase [24];
- 1,1'-dideoxygossylic acid (fig. 3, compound 23) extracted from the cotton plant was tested for its anti-HIV in *in vitro* tests. The EC_{50} was <1μM and its threshold cytotoxicity was 20 μM [25];
- monosodium and monopotassium salts (fig. 3, compounds 24, 25, 26) of isomeric caffeic acid tetramer isolated from *Arnebia euchroma* (Royle) I. M. Johnst, showed strong inhibition against HIV replication in actually infected H9 cells with EC_{50} values of 2.8, 4.0 and 1.5 μg/ml, respectively [26];
- 1,3,4,5-tetragalloylquinic acid (fig. 3, compound 27) isolated from *Lepidobotrys staudii* Engl., protected CEM-SS cells from sytopathic effect of HIV-1RF [27];
- gallic (fig. 3, compound 28) and ellagic (fig. 3, compound 29) acids isolated from *Lagerstroemia speciosa* L. inhibited HIV-1 protease and RT activity [28];
- lithospermic acid (fig. 3, compound 30) and lithospermic acid B (fig. 3, compound 31) isolated from *Salvia miltiorrhiza* Bunge, showed potent anti-HIV activities with no cytotoxicity effects to H9 cells at distinct concentrations (CC100 > 297 μM and >223 μM, respectively). The compounds suppressed the acute HIV-1 infection of H9 cells with IC_{50} values of 2 and 6.9 μM, respectively [29];
- rosmarinic acid (fig. 3, compound 32), isolated from *Coleus parvifolius* Benth. inhibited HIV-1 integrase with IC_{50} value of 5.0 μM [30, 31], whereas 2-methoxy-3-methyl-4,6-dihydroxy-5-(3'-hydroxy) cinanamoylbenzaldehyde (fig. 3, compound 33), present in *Desmos chinensis* Lour., exhibited anti-HIV activity with IC_{50} value of 0.022 μM [32].

Tannins, prenylated biphenyl and catechol

Tannins are nitrogen-free natural substances of high molecular weight, water-soluble, containing numerous hydroxyl groups, with the properties of creating permanent bonds with proteins and other macromolecules. Among these group some compounds reveal anti-HIV potential, including:
- 1,3,4,6-tetra-O-galloyl-β-D-glucose (fig. 4, compound 34) and corilagin (fig. 4, compound 35) isolated from *Chamaesyce hyssopifolia* (L.) Small, inhibited HIV-RTase [33];
- 8-C-ascorbyl(-)-epigallocatechin (fig. 4, compound 36) isolated from *Phyllanthus niruri* L. showed HIV inhibition with 9.5 as TI value [34]. Theasinensin D (fig. 4, compound 37), obtained from the same plant, demonstrated relatively strong anti-HIV activity (EC_{50} = 8 μg/ml) with therapeutic indexes of 5 [35];
- geraniin (fig. 4, compound 38) isolated from *Phyllanthus amarus* Schumach. & Thonn., showed potent anti-HIV-1 replication in MT-4 cells with an EC50 of 0.24 μg/ml and TI values of 26.8 [36];
- bergenin (fig. 4, compound 39), norbergnin (fig. 4, compound 40) and methyl norbergenin (fig. 4, compound 41) obtained from *Ardisia japonica* (Thunb.) Blume exhibited moderate anti-HIV activities *in vitro* [37];
- similar activity was described for diprenylated bibenzyl, 5-(3-hydroxyphenethyl)-2-(3-methylbut-2-enyl)-3-(3-methylbut-2-enyloxy)phenol (fig. 4, compound 42) from *Glycyrrhiza lepidota* Pursh. [38] and peltatol A (fig. 4, compound 43) isolated from *Pothomorphe peltata* (L.) Miq. [39].

Phenylethanone, phenylethanoid glycoside and others

- mallotojaponin (fig. 5, compound 44), isolated from *Mallotus japonicas* (L.f.) Mull. Arg., inhibited HIV-1 RTase [40];
- phenylethanoid glycoside, calceolarioside B (fig. 5, compound 45), isolated from *Fraxinus sieboldiana* Blume, showed moderate binding affinity on HIV gp41 [41];

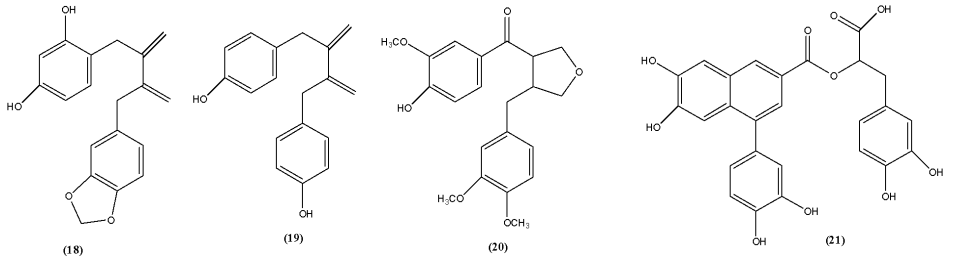

Figure 2

The chemical structures of lignans with anti-HIV activity: (18) anolignan A, (19) anolignan B, (20) (-)-arctigenin, (21) globoidnan

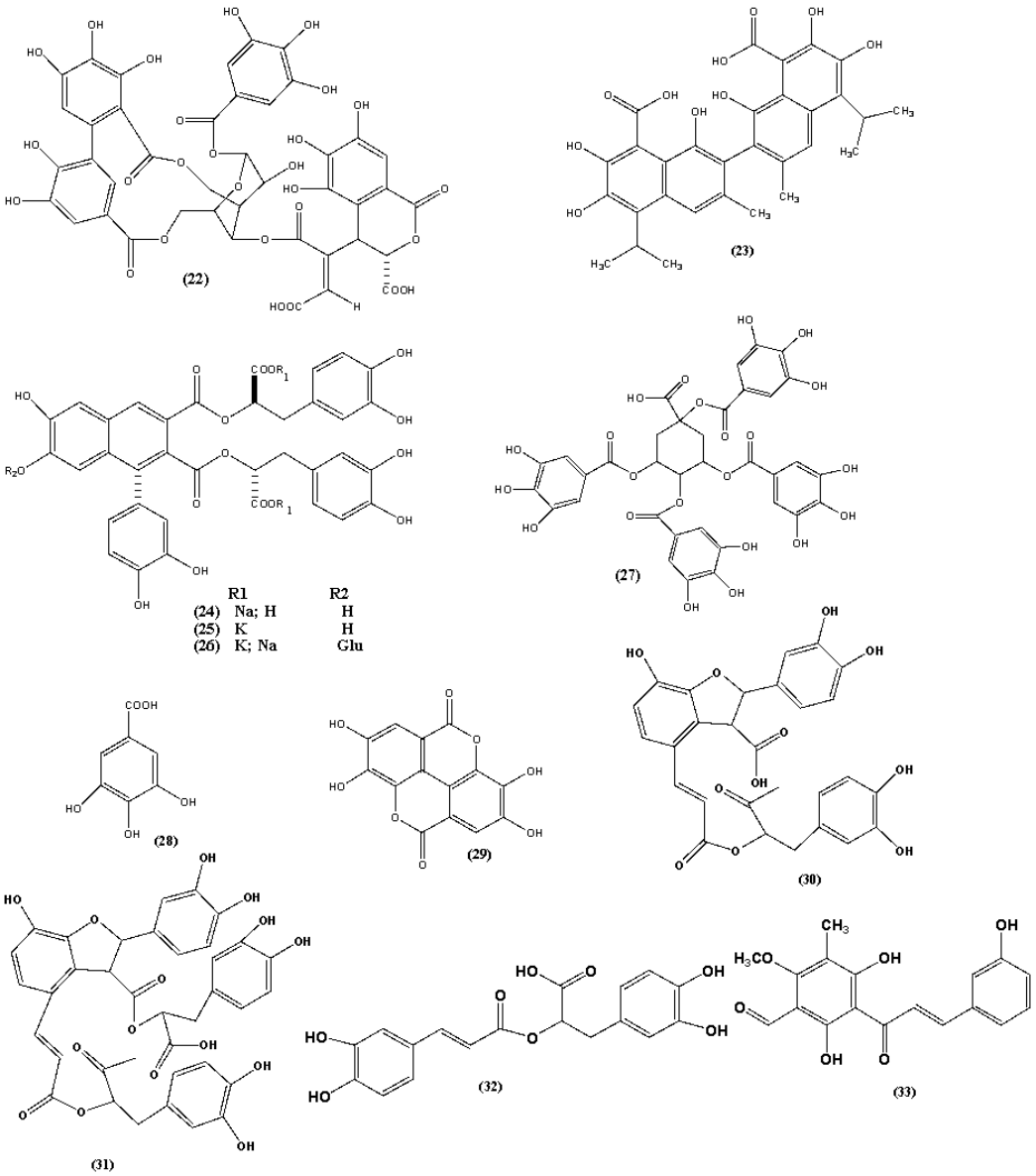

Figure 3

Chemical structures of phenolic acids, salts and phenolic aldehyde with anti-HIV activity: (22) repandusinic acid, (23) 1,1'-dideoxygossylic acid, (24-26) monosodium and monopotassium salts of isomeric caffeic acid, (27) 1,3,4,5-tetragalloylquinic acid, (28) gallic acid, (29) ellagic acid, (30) lithospermic acid, (31) lithospermic acid B, (32) rosmarinic acid, (33) 2-methoxy-3-methyl-4,6-dihydroxy-5-(3'-hydroxy)cinanamoylbenzaldehyde

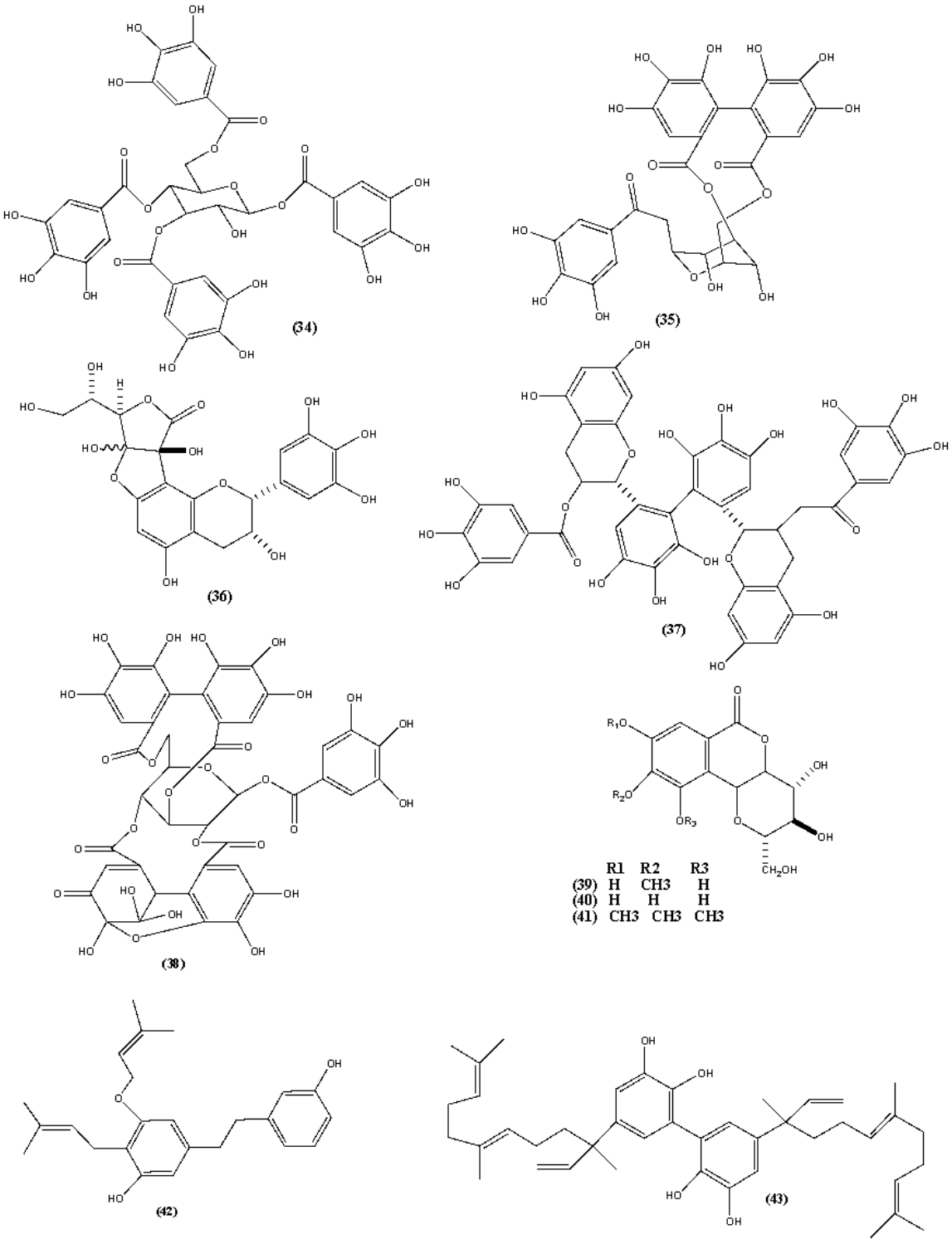

Figure 4

The chemical structures of tanins, prenylated biphenyl and catechol with anti-HIV activity: (34) 1,3,4,6-tetra-O-galloyl-β-D-glucose, (35) corilagin, (36) 8-C-ascorbyl(-)-epigallocatechin, (37) theasinensin D, (38) geraniin, (39) bergenin, (40) norbergnin, (41) methyl norbergenin, (42) 5-(3-hydroxyphenethyl)-2-(3-methylbut-2-enyl)-3-(3-methylbut-2-enyloxy)phenol, (43) peltatol A

- balanocarpol (fig. 5, compound 46), dimeric resveratrol obtained from *Hopea malibato* Foxw., showed moderate anti-HIV activity in the antiviral assay [42];
- resveratrol (fig. 5, compound 47) isolated from *Smilax china* L., in targeting host nucleotide biosynthesis inhibited emtricitabine-resistant HIV-1 [43];
- a polycyclic aromatic anthraquinone derivative, hypericin (fig. 5, compound 48) isolated from *Hypericum perfratum* L., demonstrated activity against non-human and human retroviruses in lymphocytes and inhibition of HIV-RTase [44];
- macluraxanthone B (fig. 5, compound 49) from *Maclura tinctoria* (L.) Don ex Steud, exhibited moderate anti-HIV activity [45], while guttiferone A (fig. 5, compound 50) from *Symphonia globulifera* L. showed CEM-SS cells cytoprotection during HIV-1 infection [46].

CONCLUSIONS

Medicinal plants are a rich source of phenolic compounds with potential antiviral activity. They are found both in underground and above-ground plant organs. Among these compounds, flavonoids are the greatest and the most diverse in terms of anti-HIV activity. The mechanism of action of plant phenolics is related largely to the inhibition of viral enzymes activity, including transcriptases.

Ethical approval: The conducted research is not related to either human or animal use.

Conflict of interest: Authors declare no conflict of interest.

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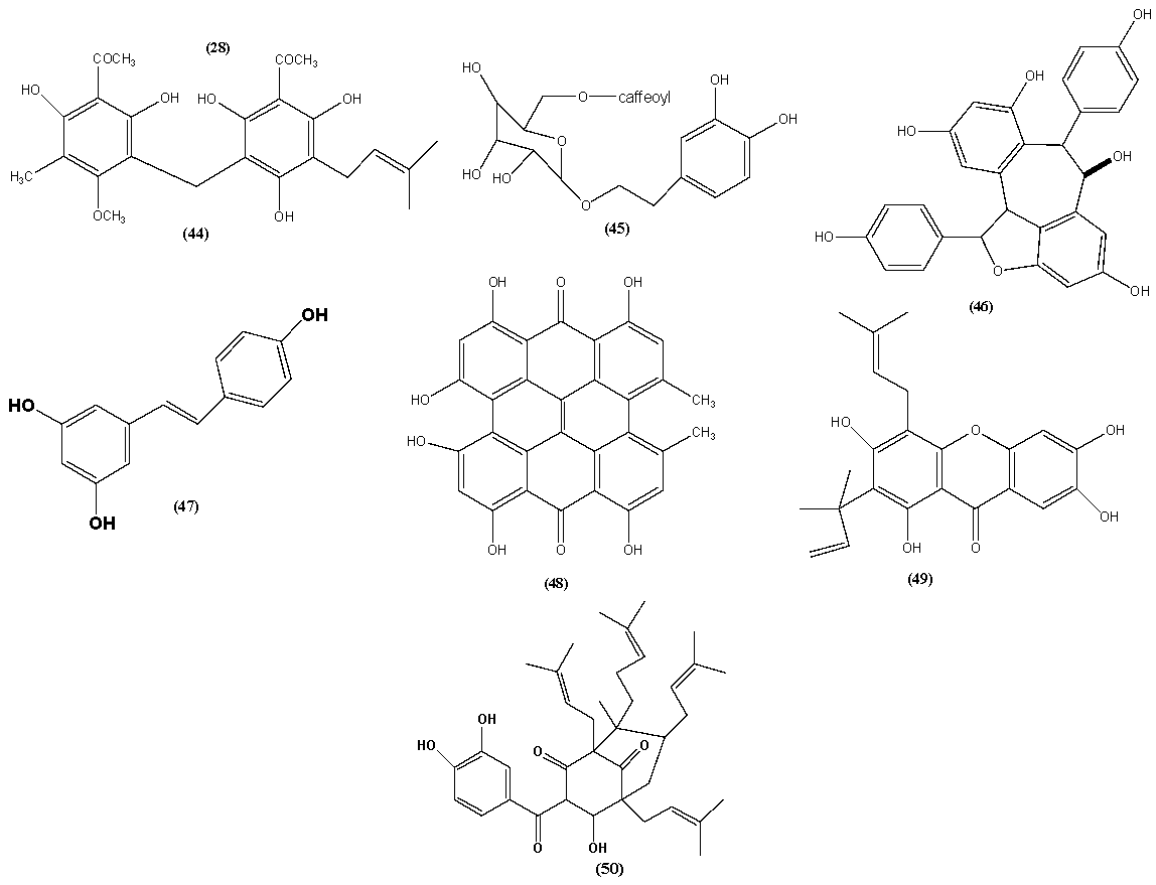

Figure 5

The chemical structures of phenylethanone, phenylethanoid glycoside and others with anti-HIV activity: (44) mallotojaponin, (45) calceolarioside B, (46) balanocarpol, (47) resveratrol, (48) hypericin, (49) macluraxanthone B, (50) guttiferone A

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