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Review Article

## Anti-HIV flavonoids from natural products: A systematic review

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### ABSTRACT

Acquired immunodeficiency syndrome could be an immunosuppressive disease (AIDS) that is produced through human immunodeficiency virus (HIV). AIDS is one of the main causes for death in Asia, Southeast Asia, and Sub Saharan Africa. Around the world, it's fourth largest killer. Almost all of the marketed, medically useful anti -HIV drugs were nucleoside; however, there usage is limited because of the serious adverse effect, drug resistance, and toxicity. The most of the drugs for several ailment diseases undergo first pass metabolism, leading to drug inactivation and also the generation of toxic metabolites. Hence, herbal medicines are generally used for alternative therapy by people live with HIV. Natural products constantly provided a source of lead compound for most disease. Flavonoids which have strong anti -HIV activities had been discussed in this article. Flavonoids are common as well as distributed group of phenolic compounds, occurring in all plant parts. Flavonoid compounds describe an essential natural source of anti-retroviral for the AIDS therapy because of their significant anti -HIV 1 activity and also low toxicity. Numerous flavonoids possess the free radical scavenging capacity, anti -inflammatory, hepatoprotective, antioxidant and anticancer activities while someone exhibit antiviral activities. The purpose of the current review is reporting the latest findings, and updates to anti-HIV flavonoids from herbal products.

**Keywords:** Anti-HIV; flavonoids; medicinal plants; mechanism of action; natural products.

### INTRODUCTION

Viruses can be an etiological agent in infective disease in human being and various other animals, are really a diverse group of infective agents which differs considerably in shape, size, chemical composition, effects on hosts and host range. AIDS is a disease for the human immune system spread out through HIV (Sepkowitz KA, 2001). HIV is mainly transmitted through hypodermic needles, unprotected sexual intercourse, contaminated blood transfusions, from mother to child during pregnancy. HIV does not transmit through saliva, and tears (CDCP, 2003). AIDS can't be cured, however antiretroviral therapy could slow the course of disease, and cause too near normal life expectancy. Antiretroviral therapy decreases the potential risk of deaths, which drugs can be very expensive and produce the severe side effects. Without antiretroviral therapy, an average survival time period after infection is calculated about 9 to 11 years, with respect to the type of HIV (UNAIDS, 2007). HIV categorized into two types like HIV 1, and HIV 2. Each originated from nonhuman primates in

West-central Africa during the 20<sup>th</sup> century. HIV 1 is originating from Chimpanzees and HIV 2 is originating from Old World Monkey (Sharp PM *et al.*, 2011). AIDS was initially identified by the United States Centers for Disease Control and Prevention (CDC) in 1981, and it is causing the HIV infection had been identified during the early part of the decade. At the time of 2012, AIDS has leads to an estimated 36 million deaths around the world, and around 35.3 million individual live with HIV all over the world (Gallo RC, 2006).

Varieties of chemical substance were assessed for inhibitory effects upon HIV replication in *in-vitro*. HIV has two main targets in *in-vivo* like tissue macrophages and CD4 lymphocytes. The treatments targeted at the control of HIV replication in the both cell types. The replicative cycle of HIV consists of ten steps that might be considered desirable targets for the treatments of HIV. A number of research laboratories are involved in the development of antiviral agents which affect with HIV in different stages of viral replication. Many of the anti-HIV substances are allotted to one among these ten classes of HIV inhibitors, based on the stage from which they interfere with the HIV replication cycle, like fusion, adsorption, uncoating, DNA replication, integration, reverse transcription, translation, transcription, maturation, and assembly or release (Rajandeep Kaur *et al.*, 2011).

After many years of the study, only a limited number of antiviral agents are available for the treatment of dis-

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eases produced by HIV. Due to their harmful effects on a host, numerous antiviral agents are limited to topical applications. Appropriately, there's needed for the effective and safe antiviral agents having a wide spectrum of antiviral activity with decreased toxicity to host. Natural products can be an essential natural source of antiretroviral for the AIDS therapy because of their considerable anti-HIV 1 activity. Numerous natural products are used by people with AIDS in certain countries without having any scientific evidence which they have anti-HIV activity. A wide range of plants derived compounds are exhibit anti-HIV activity, like flavonoids, polysaccharides, alkaloid, lignans, terpenoids, and coumarins (Huang B *et al.*, 1997; Vlietinck AJ *et al.*, 1998; Matthee G *et al.*, 1999).

In America, around 60% of people suffer with HIV use different types of alternative or complementary medicine. Herbal medicines are used as an alternate therapy for treatment of HIV by an individual living with HIV. Natural products provided sources of lead compound for almost all disease. Natural products are important sources for the drug discovery and development of novel antiviral drugs for treatment of HIV because of their availability and low side effects. Natural flavonoids with antiviral activity were known since the 1940s (Shashank Kumar *et al.*, 2013). Flavonoids are a common and distributed group of water soluble phenolic compounds, occurring in all plant parts, particularly photosynthesizing plant cell. Flavonoids represent an essential natural source for anti-retroviral for AIDS therapy.

Flavonoids can be an important part of human plus animal diet; these are major coloring component of the flowering plants. Flavonoids composed of two benzene rings (A and B) connected through heterocyclic pyrane ring (C), those two benzene rings connected with a short three carbon chain. Among the carbons in short chain can be attached to a carbon of one of the benzene rings, via oxygen bridge or either directly, thus forming a third middle ring, that can be either five or six membered ring. Flavanoids are classified into flavones, flavanones, flavonols, catechins, chalcones, and anthocyanidins related to chemical structure (Anderesen M *et al.*, 2006).

Flavonoids were reported to show various medicinal properties (Harbone JB, 1998). One of the most interesting biological properties these compounds is their ability to inhibit HIV 1 integrase (HIV 1 IN). HIV type-1 integrase is one of the three key essential enzymes for viral replication (Nair V, 2002). Flavonoids protect plants from microbes and they are functioning as antiviral, antibacterial, and antifungal agent. The phenolic groups in flavonoids responsible for antiviral activity and that activity is further enhanced with addition of phenolic groups. Flavonoids are occurring as glycosides, aglycones, and methylated derivative. A glycone form of flavonoids seems to be more inhibitory effects of rotavirus than an aglycone form of flavonoids

(Agarwal AD, 2011). This review deals with the structural aspects flavonoids with mechanism of action against HIV.

#### Anti-HIV flavonoids from medicinal plants

Robustaflavone (Fig. 1) and Hinokiflavone (Fig. 2) were bioflavonoids separated from the *Garcinia multiflora* and *Rhus succedanea*. They were showing anti HIV 1 activity against enzyme polymerase HIV 1 reverse transcriptase with IC<sub>50</sub> values of 65 and 62 µM (Lin YM *et al.*, 1997). by Raaman, 2006.

(-)-Epigallocatechin (Fig. 3) was flavonoid separated from the green tea leaf plant of *Camellia sinensis*. (-) Epigallocatechin inhibits a number of steps in the HIV life cycle, like protease kinetics and post adsorption entry. It is showing anti-HIV activity against enzyme HIV 1 reverse transcriptase with IC<sub>50</sub> values of 0.01 to 0.02 µg/ml and in addition, (-) Epigallocatechin binds with a high affinity on CD<sub>4</sub><sup>+</sup> T-cells and further more inhibits binding of GP<sub>120</sub> into the CD<sub>4</sub><sup>+</sup> cells (Yamaguchi K *et al.*, 2002; Williamson MP *et al.*, 2006).

Prenylated anti-HIV flavonoids, 6,8-diprenylkaempferol (Fig. 4) and 6,8-diprenylaromadendrin (Fig. 5) were separated from the extract of *Monotes africanus*. They were showing anti-HIV *inhibitory* activity in XTT based and whole cell screen assay (Meragelman KM *et al.*, 2001).

Quercetin 3-O-(2-galloyl) α-L-arbinopyranose (Fig. 6) was flavonoid, separated from the plant extract of *Acer okamotoanum*, which have anti-HIV-1 integrase activity with IC<sub>50</sub> values of 18.1±1.3 µg/ml (Kim HJ *et al.*, 1998).

Wikstroel B (Fig. 7) was bi flavonoid separated from the roots extract of *Wikstroemia indica*, exhibited the good anti-HIV 1 activity in *in-vitro* studies (Hu K *et al.*, 2000).

Pterocarpan (Fig. 8) was flavonoid separated from the extract of *Erythrina*, exhibited good anti-HIV 1 activity in *in-vitro* studies (McKee TC *et al.*, 1998).

Xanthohumol (Fig. 9) was prenylchalcone separated from hops of *Humulus lupulus*. It inhibits HIV-1 induced cytopathic effects, the production of viral p24 antigen and the enzyme reverse transcriptase in C8166 lymphocytes with EC<sub>50</sub> values of 0.82, 1.28 and 0.50 µg/ml and also inhibited HIV 1 replication in peripheral blood mononuclear cells with EC<sub>50</sub> value of 20.74 µg/ml (Wang Q *et al.*, 2004).

2-methoxy-3-methyl-4, 6-dihydroxy-5-(3'-hydroxy) cinnamoylbenzaldehyde (Fig. 10) and lawinal (Fig. 11) were chalcone and flavonone respectively separated from the root extract of *Desmos*. They were showing potent anti-HIV activity with IC<sub>50</sub> values of 0.022 and 2.30 µg/ml (Wu JH *et al.*, 2003).

Luteolin (Fig. 12) and luteolin-7-methyl ether (Fig. 13) were flavonoids separated from the extract of aerial parts of *Coleus parvifolius*, exhibited anti-HIV1 inte

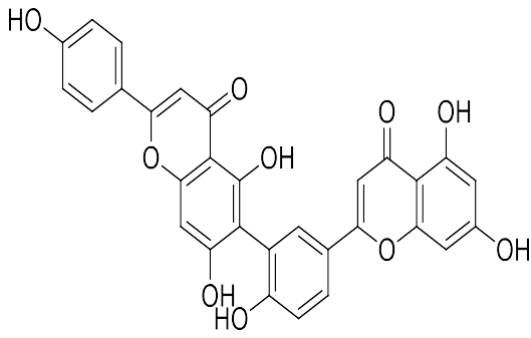


Figure 1: Robustaflavone

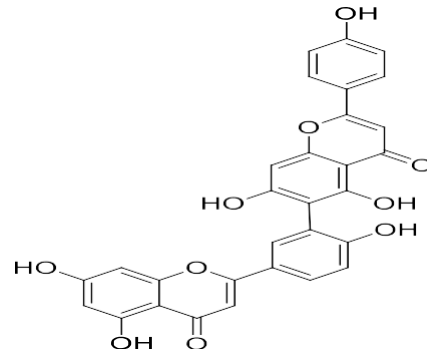


Figure 2: Hinokiflavone

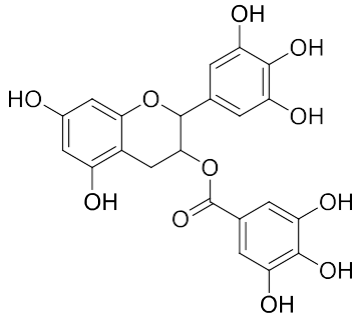


Figure 3: (-) Epigallocatechin

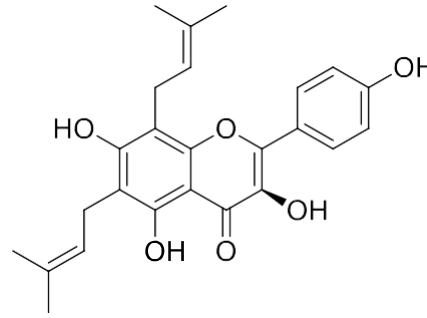


Figure 4: 6,8-Diprenylkaempferol

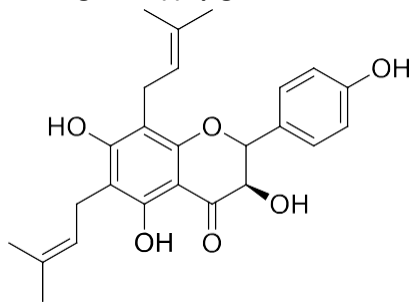


Figure 5: 6,8-Diprenylaromadendrin

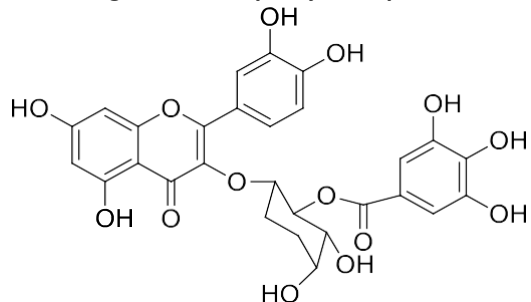


Figure 6: Quercetin 3-O-(2-galloyl) a-L-arbinopyranose

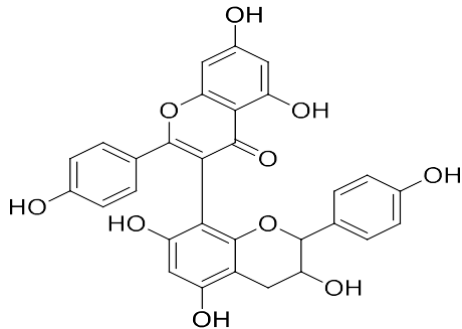


Figure 7: Wikstroel B

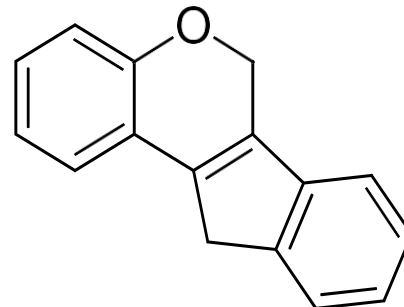


Figure 8: Pterocarpans

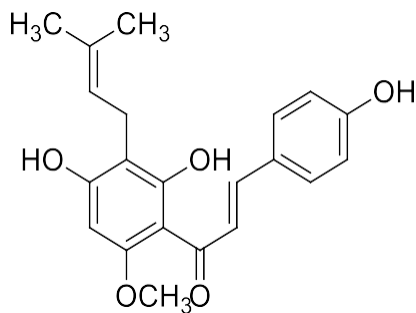


Figure 9: Xanthohumol

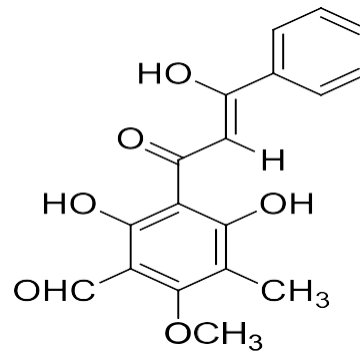
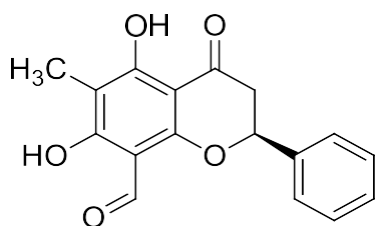
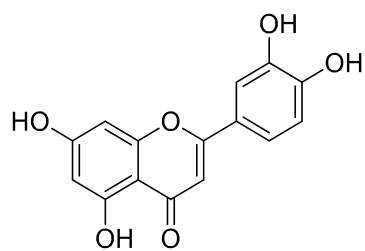


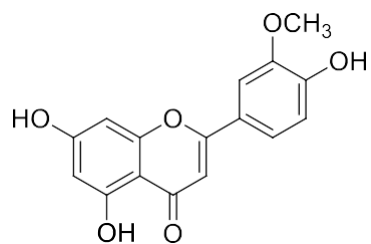
Figure 10: 2-Methoxy-3-methyl-4,6-dihydroxy-5-(3'-hydroxy) cinnamoyl benzaldehyde



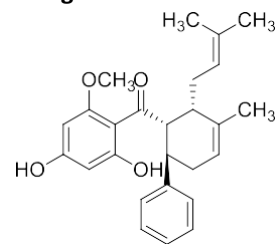
**Figure 11: Lawinal**



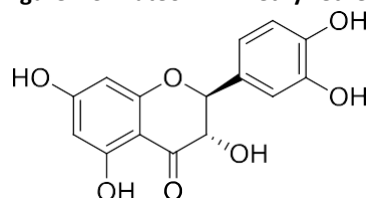
**Figure 12: Luteolin**



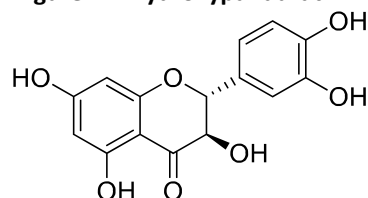
**Figure 13: Luteolin-7-methyl ether**



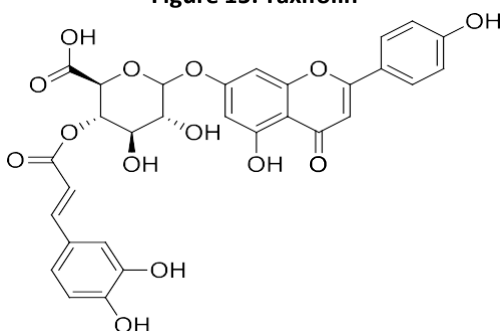
**Figure 14: Hydroxypanpuratin A**



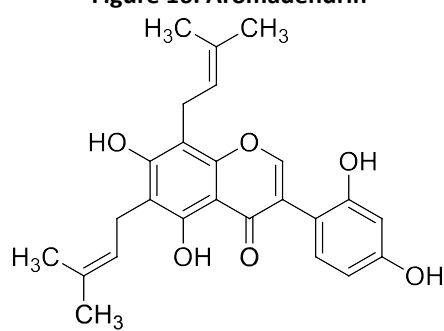
**Figure 15: Taxifolin**



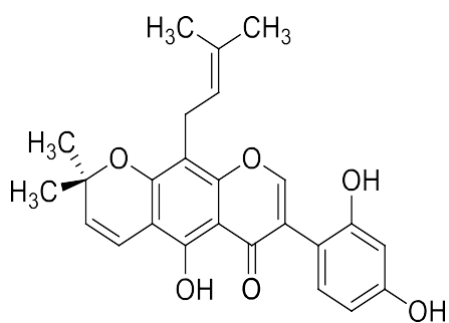
**Figure 16: Aromadendrin**



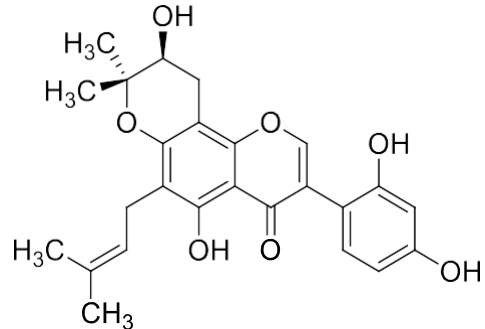
**Figure 17: Apigenin 7-O-beta-D-(4'-caffeoyl) glucuronide**



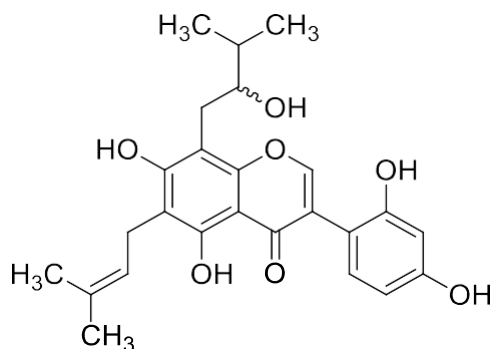
**Figure 18: 8-Prenylluteone**



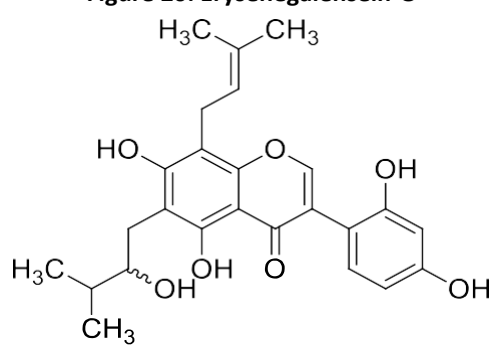
**Figure 19: Auriculatin**



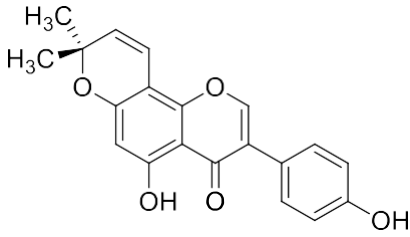
**Figure 20: Erysenegalensein O**



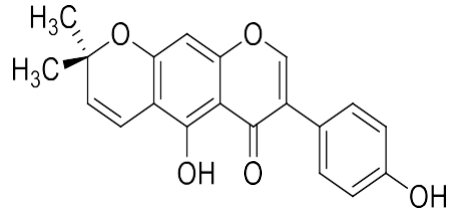
**Figure 21: Erysenegalensein D**



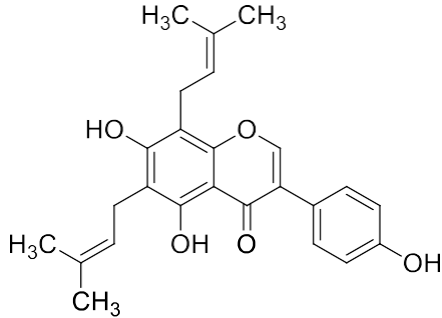
**Figure 22: Erysenegalensein N**



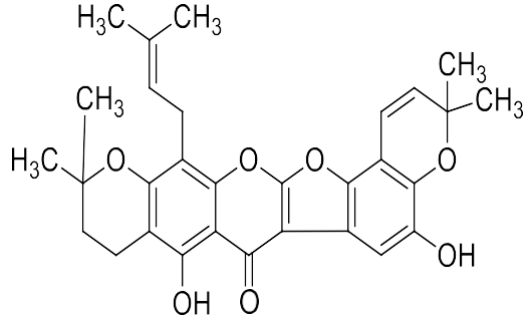
**Figure 23: Derrone**



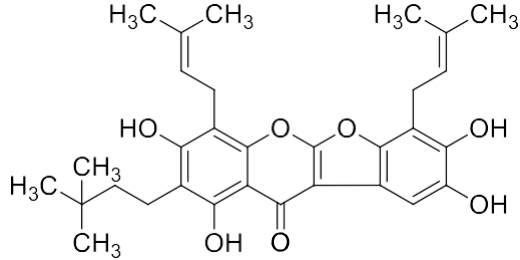
**Figure 24: Alpinumisoflavone**



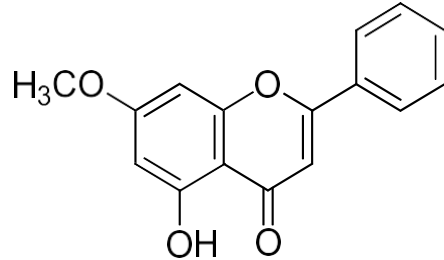
**Figure 25: 6,8-Diprenylgenistein**



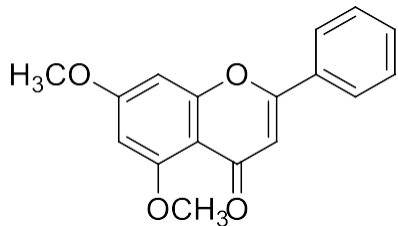
**Figure 26: Formosanatin C**



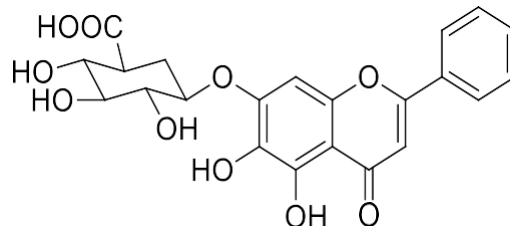
**Figure 27: Euchretin M**



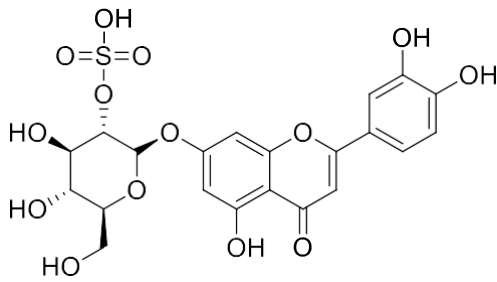
**Figure 28: 5-Hydroxy-7-methoxyflavone**



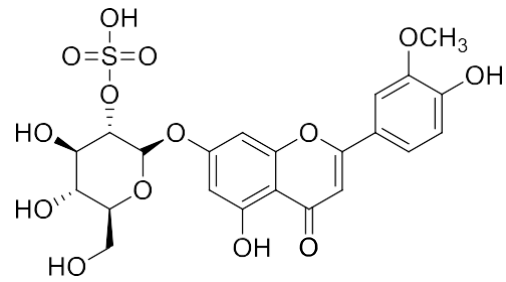
**Figure 29: 5,7-Dimethoxyflavone**



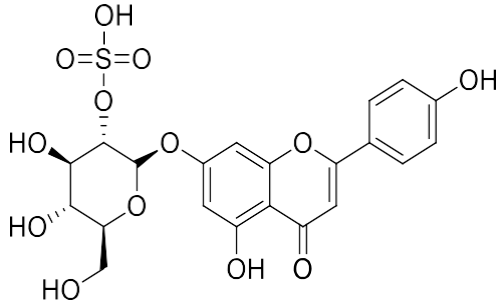
**Figure 30; Baicalin**



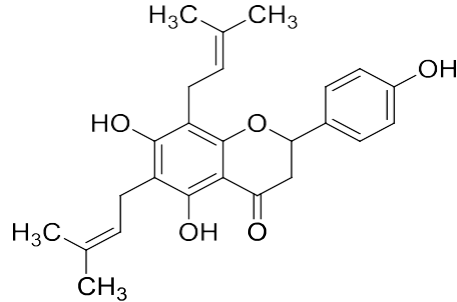
**Figure 31: Thalassiolins A**



**Figure 32: Thalassiolins B**



**Figure 33: Thalassiolins C**



**Figure 34: Lonchocarpol A**

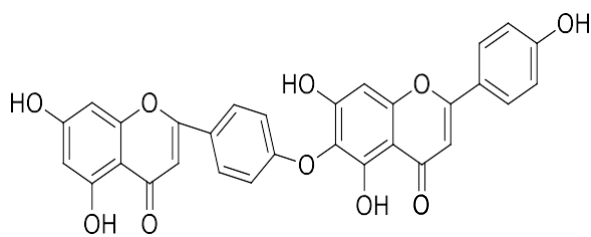


Figure 35: Ochnaflavone 7''-O-methyl ether

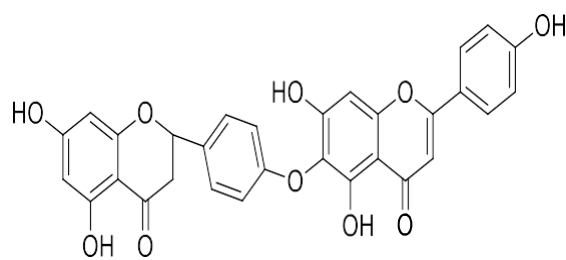


Figure 36: 2'', 3''-dihydrochnaflavone 7''-O-methyl ether

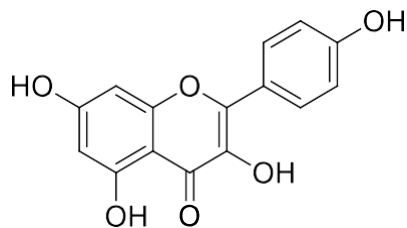


Figure 37: Kaempferol

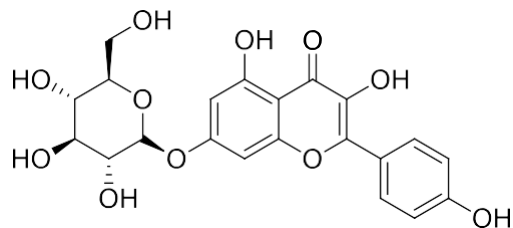


Figure 38: Kaempferol-7-O-glucoside

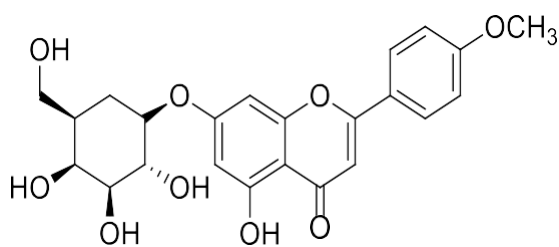


Figure 39: Acacetin-7-O-β-D-galactopyranoside

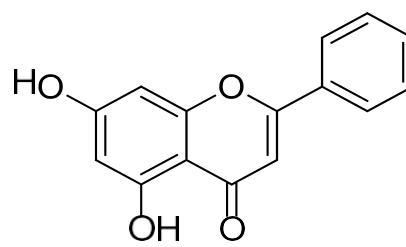


Figure 40: Chrysin

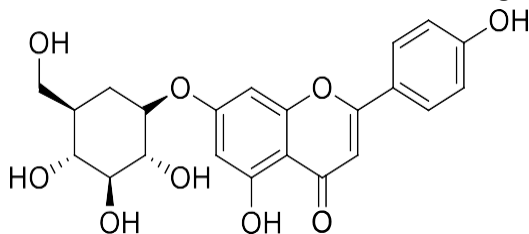


Figure 41: Apigenin-7-O-β-D-glucopyranoside

grase activity with  $IC_{50}$  values of  $11\mu M$  (Tewtrakul S *et al.*, 2003).

Hydroxypanduratin A (Fig. 14) was chalcone separated from the extract of rhizomes of *Boesenbergia pandurata*, which exhibited the anti-HIV 1 protease activity with  $IC_{50}$  values of  $5.6\mu M$  (Cheenpracha S *et al.*, 2006).

Taxifolin (Fig. 15) was flavonoid separated from of *Juglans mandshurica*, which exhibited the most potent HIV induced cytopathic activity against MT-4 cells with  $IC_{100}$  value of  $25\mu g/ml$  and also inhibited the enzymes protease and reverse transcriptase (Byung Sun Min *et al.*, 2002).

Aromadendrin (Fig. 16) was flavonoid separated from the *Cuscuta reflexa*. It was inhibited the CD4/gp120 interaction by binding to the V3 loop of gp120, but not inhibited the enzymes protease and reverse transcriptase (Mahmood N *et al.*, 1997).

Apigenin 7-O-beta-D-(4'-caffeoyl) glucuronide (Fig. 17) was new flavonoid separated from the extract of flowers of *Chrysanthemum morifolium*, which exhibited the strong HIV 1 integrase inhibitory activity with  $IC_{50}$  val-

ues of  $7.2 \pm 3.4 \mu g/ml$  and anti-HIV activity with  $EC_{50}$  values of  $41.86 \pm 1.43 \mu g/ml$  in MTT based whole cell culture assay using the HIV 1 (IIIB) infected MT-4 cells (Lee JS *et al.*, 2003).

8-prenylfluteone (Fig. 18), auriculatin (Fig. 19), erysenegalsein O (Fig. 20), erysenegalsein D (Fig. 21), erysenegalsein N (Fig. 22), derrone (Fig. 23), alpinumisoflavone (Fig. 24), and 6, 8-diprenylgenistein (Fig. 25) were prenyliso flavonoids separated from *Erythrina senegalensis*. They were showing the dose dependent inhibitory activities on HIV-1 protease with  $IC_{50}$  values of 4.0, 3.5, 5.0, 2.5, 4.5, 18.2, 30.1, and 0.5 respectively (Lee J *et al.*, 2009).

Formosanatin C (Fig. 26) and euchretin M (Fig. 27) were flavonoids isolated from *Euchresta formosana*, which compounds inhibited the HIV replication in H9 lymphocyte cells (Lo WL *et al.*, 2003).

5-Hydroxy-7-methoxyflavone (Fig. 28) and 5, 7-dimethoxyflavone (Fig. 29) were flavonoids separated from the plant *Kaempferia parviflora*, which flavanoids

inhibited the HIV 1 protease with IC<sub>50</sub> values of 19 μM (Geitmann M et al., 2006).

Baicalin (Fig. 30) was flavonoid separated from *Scutellaria baicalensis*, which inhibits the HIV 1 replication in PBMC and enzyme HIV 1 reverse transcriptase with IC<sub>50</sub> values of 0.2-0.5 μg/ml and IC<sub>50</sub> values of 2 μg/ml respectively (Li BQ et al., 1993).

Thalassiolins A (Fig. 31), thalassiolins B (Fig. 32) and thalassiolins C (Fig. 33) were flavonoids separated from the *Thalassia testudinum*, inhibit the enzyme HIV 1 integrase with IC<sub>50</sub> values of 0.4-2.0 μM (Kaleab Asres et al., 2005).

Lonchocarpol A (Fig. 34) was prenylated flavonoid separated from the *Monotes africanus*, that inhibit the HIV in XTT based whole cell screen assay (Meragelman KM et al., 2001).

Ochnaflavone 7"-O-methyl ether (Fig. 35) and 2", 3"-dihydroochnaflavone 7"-O-methyl ether (Fig. 36) were flavonoids separated from the twigs and leaves of *Ochna integerrima*, which inhibit the enzyme HIV 1 reverse transcriptase with IC<sub>50</sub> values of 2.0 and 2.4 μg/mL, respectively (Reutrakul V et al., 2007).

Kaempferol (Fig. 37) and kaempferol -7-O-glucoside (Fig. 38) were flavonoids separated from the *Securigera securidaca*, which inhibited the enzyme reverse transcriptase with IC<sub>50</sub> values of 50 and 32 μg/ml, respectively (Behbahani M et al., 2014).

Acacetin-7-O-β-D-galactopyranoside (Fig. 39) was glycosyloxyflavone separated from the flowering heads of plant *Chrysanthemum morifolium*, have been found to exhibit anti-HIV activity (Hui-Kang Wang et al., 1998).

Chrysin (Fig. 40), as well as apigenin-7-O-β-D-glucopyranoside (Fig. 41) was separated from the *Kummerowia striata*, have been found to exhibit anti-HIV activity (Hui-Kang Wang et al., 1998).

## CONCLUSION

The present review article covers the anti-HIV flavonoids present in the natural product and mechanism of action. Flavonoids are plant pigments that inhibit the many bacterial strains and viral enzymes, like protease, and reverse transcriptase. Physicians are increasing use of flavonoids to treat HIV, because of their proven ability to inhibit the specific enzymes. A number of synthetic anti-viral drugs are launched in the market to treat the HIV, but flavonoids from natural product are lesser side effects, easy accessibility and low cost. In future, such study claims an open area of research, for sound consideration for the development of new drugs for the treatment of HIV.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest

## ACKNOWLEDGEMENTS

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