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REVIEW

Role of phytocompounds as the potential anti-viral agent: an overview

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Abstract

Viral diseases are the most notorious infective agent(s) causing morbidity and mortality in every nook and corner for ages; viruses are active in host cells, and specific anti-virus medicines' developments remain uncanny. In this century of the biological era, human viruses act predominantly as versatile spreaders. The infection of the present COVID-19 virus is up in the air; blithely, the integument of medicinal chemistry approaches, particularly bioactive derived phytocompounds could be helpful to control those human viruses, recognized in the last 100 years. Indeed, natural products are being used for various therapeutic purposes. The major bioactive phytocompounds are chemically containing coumarin, thiosulfonate, steroid, polysaccharide, tannin, lignin, proanthocyanidin, terpene, quinone, saponin, flavonoid, alkaloid, and polyphenol, that are documented for inhibitory action against several viral infections. Mostly, about 20–30% of plants from tropical or temperate regions are known to have some antiviral activity. This comprehensive analysis of bioactive-derived phytocompounds would represent a significant impact and might be helpful for antiviral research and the current state of viral treatments.

Keywords Phytochemicals · Natural product · COVID-19 · Antiviral · Viral infection disease · SAR studies

Introduction

For decades, active ingredients from fresh parts and solvent-processed plant extracts have been used in mainstream medicines in every culture. However, plant extracts have several secondary metabolites for therapeutic utility as pharmaceuticals, but today, herbal medicines are exploited for drug development cascades. Thus, it is important to know about potential phytoactive compounds with antiviral properties, in this pandemic COVID-19 time. Moreover, viral diseases (Huerta-Reyes et al. 2022) cause mild to severe acute human respiratory illnesses. The liver-damaging hepatitis A, B, and C viruses and several other viruses, including Zika, chikungunya, dengue, herpes simplex virus (HSV), and a few more, have caused consternation in human health in the last four decades. Indeed, viruses have comparatively faster-mutating rates, resulting in suitably surviving strains that pose significant hazards to humanity (Kapoor et al. 2017). There is a regular advent of novel and versatile viral strains that survive the hard preventive measures, which had been addressed by newly identified anti-viral agent(s) with lesser side effects/host toxicity, in the past.

Several lethal viruses have recently caused pandemics, and a few more drugs have been located/produced to effectively treat those viral diseases (Li et al. 2022; Mohanty et al. 2021; Issa et al. 2022; Beck et al. 2013). Most of the anti-viral medicines have detrimental failures with long-term drug resistance. Various plants are valuable assets, which are to be explored, especially in emerging resistant infectious diseases (Idriss et al. 2023a, b; Mukhtar et al. 2008). Undeniably, plant-derived phytoactive compounds are potential therapeutic metabolites with the power to obstruct, control viral uptake, attach to surface receptors, and compete for pathways of activation of intracellular signals (Mao et al.

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2022; Ghosh et al. 2009; Kapoor et al. 2017; Khan et al. 2005; Mohapatra and Dar 2010).

Furthermore, plant-derived phytoactive compounds are the most wanted items in pharmacology to investigate, extract active ingredients, and demonstrate the inherent therapeutic properties. Currently, phytochemicals are conjugated with nanoparticles to increase their efficacy against several diseases (Bakrim et al. 2022; Goktas et al. 2020), and a similar conjugated nanoparticles approach can be taken against infectious viral diseases to increase the potency of phytoactive compounds. However, only about 25% of phytocompounds are used as drugs (Cragg and Newman 2005; Kapoor et al. 2017). Moreover, since time immemorial, phytocompounds from around 2500 meditational plant species had been recorded as traditional medicines (De Smet 2002; Shinwari 2010) (Fig. 1). The major bioactive phytocompounds are coumarins, thiosulfonates, steroids, polysaccharides, tannins, lignins, proanthocyanidins, terpenes, quinones, saponins, flavonoids, alkaloids, and polyphenols, which are known to fight several viral infections (Kapoor et al. 2017). Mostly, about 20–30% of plants from tropical or temperate regions are known to have some antiviral activity (Roumy et al. 2020; Perez 2003). In this review, some bioactive phytochemicals with antiviral activity are described, which might be helpful for antiviral research.

Utility of phytoactive compound for emerging viral diseases

Emerging diseases from viral infections, especially in this era, are a serious challenge to humanity. Phytochemicals with broad-spectrum anti-viral effects could be used to discover novel drugs for such dreadful infectious diseases causing a pandemic. Some examples such as *Lindera aggregate*, *Pyrrosia lingua*, *Artemisia annua*, *Myrica cerifera*, *Curcuma longa*, *Rheum palmatum*, *Phaseolus vulgaris*, *Amaranthus tricolor*, *Citri reticulatae pericarpium*, *Erigeron breviscapus*, *Fraxinus sieboldiana*, *Hyptis atrorubens Poit*, *Camellia sinensis*, *Phyllanthus emblica*, *Lycoris radiate*, *Glycyrrhiza uralensis*, *Glycyrrhiza radix*, *Psorothamnus arborescens*, and *Scutellaria baicalensis* appeared to have

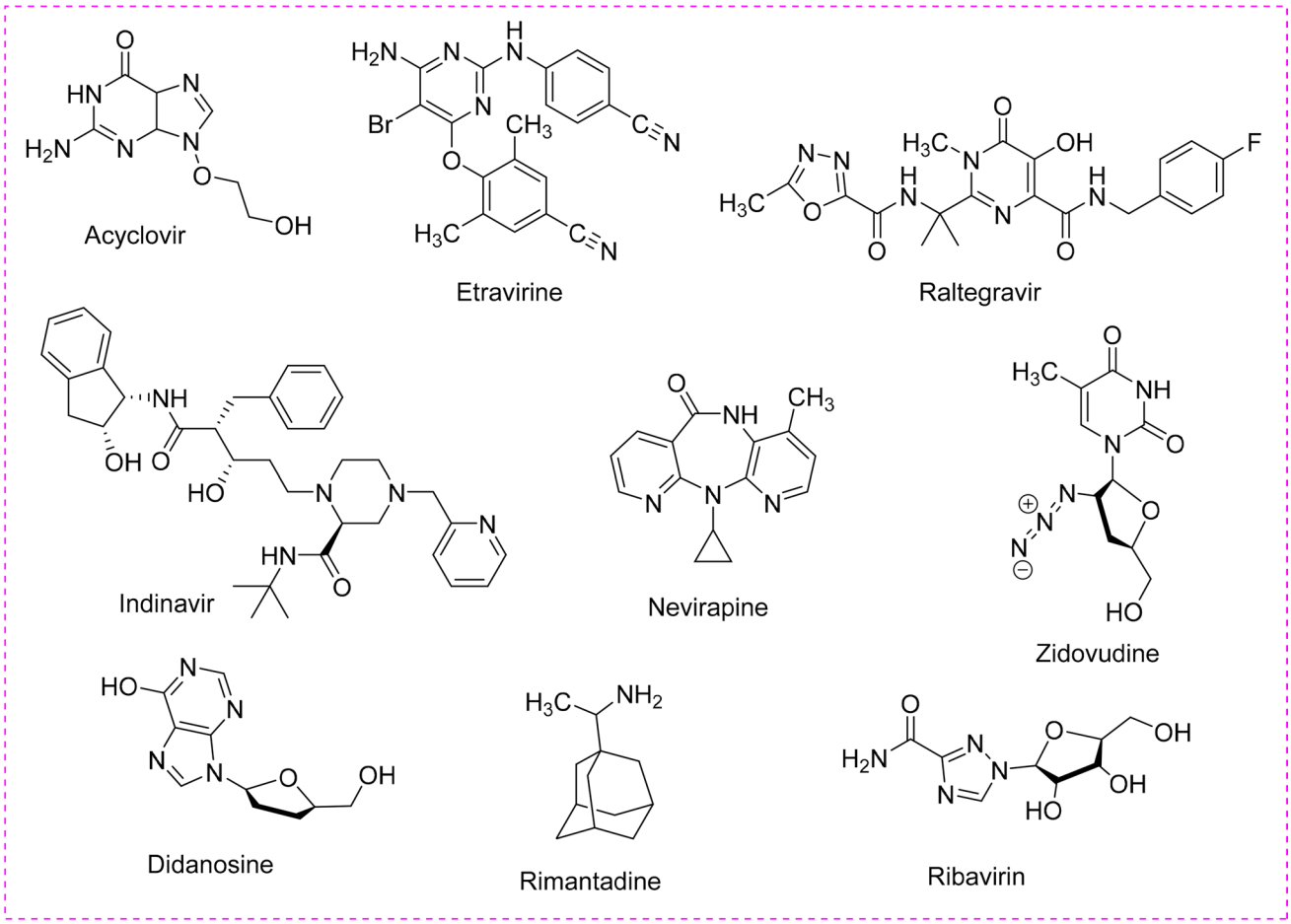


Fig. 1 Synthetic commercially available several classes of antiviral drugs

Table 1 List of phytoactive compounds' inhibitory action against viral diseases

Sl. No	Plant name	Phytoactive compound	Effective against	Reference
1	*Actinodaphne hookeri*	Actinophnine	HSV-1	(Perez 2003)
2	*Flindersia fournieri* and *Flindersia amboinensis*	Alkaloids	ZIKV	(Byler et al. 2016)
3	*Atropa belladona* L	Atropine	All enveloped viruses	(Perez 2003)
4	*Euodia roxburghiana*	Buchapine	HIV-1	(Perez 2003)
5	*Ophiorrhiza mungos*	Camptothecin, 10-methoxycamptothecin	HHV	(Perez 2003)
6	*Commelina communis*	Homonojirimycin	H1N1	(Ghildiyal et al. 2020; Zhang et al. 2013)
7	*Carnavalia ensiformis* L	Canavanin	Influenza virus, Semliki Forest virus	(Perez 2003)
9	*Theobroma cacao* L	Caffeine	Coxsackie-virus, Echonovirus, Herpes, Poliovirus, vaccinia, influenza virus	(Perez 2003)
10	*Cassia siamea*	Cassiarin D	ZIKV	(Byler et al. 2016)
11	*Chelidonium majus* L	Chelidonine	HHV, influenza virus	(Perez 2003)
12	*Cordyceps militaris*	Cordycepin	picornavirus, poliovirus, vaccinia, newcastle disease virus, HSV, influenza viruses	(Perez 2003)
13	*Mammea americana* and *Tabernaemontana cymosa*	Coumarin	CHIKV DENV	(Gómez-Calderón et al. 2017)
14	*Cryptocarya pleurosperma*	Cryptopleurine	HSV-1	(Perez 2003)
15	*Curcuma longa*	Curcumin	EBOV	(Baikerikar 2017)
16	*Buchenavia capitata*	*O*-Demethyl-buchenavianine	HIV	(Perez 2003)
17	*Cephaelis ipecacuanha*	Emetine	HHV, Semliki Forest virus	(Perez 2003)
18	*Camellia sinensis*	Epigallocathechin-3-gallate	HBV	(Ben-Shabat et al. 2020)
19	*Fagara zanthoxyloides* Lam	Fagaronine	All retrovirus	(Perez 2003)
20	*Flindersia acuminata*	Flinderole A	ZIKV	(Byler et al. 2016)
21	*Peganum harmala*	Harmaline, harmine	HSV-1	(Perez 2003)
22	*Clivia miniata*	Lycorine	several RNA and DNA viruses	(Perez 2003)
23	*Lycoris radiata*	Lycorine	SARS-CoV	(Mani et al. 2020)
24	*Boenninghausenia sessilicarpa*	Leptodactylone	SARS-CoV	(Mani et al. 2020; Yang et al. 2007b)
25	*Vaccinium macrocarpon* *Calamus scipionum* *Allium sativum*	Myricetin	SARS-CoV	(Mani et al. 2020)
26	*Scutellaria baicalensis*	Scutellarein	SARS-CoV	(Mani et al. 2020)
27	*Ancistrocladus korupensis* D	Michellamines D and F	HIV	(Perez 2003)
28	*Camptotheca acuminata*	10-Methoxycamptothecin	Adenovirus, herpes, and vaccinia viruses	(Perez 2003)
29	*Polyathia oliveri*	Oliverine	HSV-1	(Perez 2003)
30	*Stephania japonica*	Oxostephanine	HSV-1	(Montanha et al. 1995; Perez 2003)
31	*Pachypodanthium staudti*	Pachystaudine	HSV-1	(Montanha et al. 1995; Perez 2003)
32	*Papaver somniferum*	Papaverine	Cytomegalovirus (CMV), measles, HIV, and several other viruses	(Manske and Holmes 2014; Perez 2003)
33	*Cephaelis acuminata*	Psychotrine	HIV-1	(Perez 2003)
34	*Schumanniophyton magnificum*	Schumannificine	HIV HSV	(Mukherjee 2019; Perez 2003)
35	*Camellia sinensis*	Theaflavin	SARS-CoV-2	(Lung et al. 2020; Mani et al. 2020)

Table 1 (continued)

Sl. No	Plant name	Phytoactive compound	Effective against	Reference
36	*Arachniotus aureus* (Eidam) Schoeter and *Aspergillus terreus*	Aranotin, gliotoxin	Poliovirus, rhinovirus, influenza virus, para-influenza virus type 3	(Perez 2003)
37	*Castanospermum australe*	Castanospermine, Australine	HIV	(Perez 2003)
38	*Catharanthus roseus* L. G. Don *C. lanceus* Pich	Leurocristina, periformyline, perivine, vincaleucoblastine	Poliovirus, vaccinia, influenza viruses	(Perez 2003)
39	*Berberis vulgaris*	Columbamine, berberine, palmitine	HIV-1	(Manske and Holmes 2014; Perez 2003)
40	*Buxus sempervirens*	Buxamine E, cyclobuxamine H	HIV-1	(Perez 2003)
41	*Jatropha multifida* L	Multifidone, multifidanol, multifidenol, and jatrophone	Influenza virus	(Shoji et al. 2017)
42	*Andrographis paniculata, Curcuma longa*, *Gynostemma pentaphyllum, Kaempferia parviflora*, *Psidium guajava*	5,7-Dimethoxyflavone, Trimethylapigenin, Tetramethylluteolin	Influenza virus	(Sornpet et al. 2017)
43	*Scutellaria baicalensis*	Baicalin	DENV	(Kapoor et al. 2017; Moghaddam et al. 2014)
44	*Glycyrrhiza inflate*	Chalcones	Influenza virus	(Dao et al. 2011; Kapoor et al. 2017)
45	*Aglaia* sp.	Dammarenolic acid	Retroviruses	(Esimone et al. 2010)
46	*Croton mauritianus*	Decanoylphorbol-13 acetate	CHIKV	(Corlay et al. 2014)
47	*Phyllanths urinaria*	Excoecariani, loliolide	HSV- 2, Hepatitis C (HCV)	(Chung et al. 2016)
48	*Ziziphus jujuba*	Jubanines	Porcine epidemic diarrhea virus (PEDV)	(Kang et al. 2015)
49	*Swietenia macrophylla*	Limonoids	HCV	(Cheng et al. 2014)
50	*Camellia japonica*	Oleanane	PDEV	(Yang et al. 2015)
51	*Embelia ribes*	Quercetin	HCV	(Kapoor et al. 2017)
52	*Bupleurum kaoi*	Saikosaponins	HCV	(Lin et al. 2015)
53	*Rheum palmatum*	Sennoside A	HIV-1	(Esposito et al. 2016)
54	*Aglaia foveolata*	Silvestrol	EBOV	(Biedenkopf et al. 2017)
55	*Schisandra micrantha*	SJP-L-5	HIV-1	(Bai et al. 2015)
56	*Tanacetum vulgare*	Swerilactones	HSV-1 HSV-2	(Álvarez et al. 2015)
57	*Humulus lupulus*	Xanthohumol	BVDV	(Kapoor et al. 2017)
58	*Artocarpus lakoocha*	Oxyresveratrol	HSV-1 HSV-2	(Kapoor et al. 2017)
59	*Bupleurum kaoi*	Saikosaponin b2	HCV	(Xu et al. 2014)
60	*Citrus reticulate*	Tangeretin and nobiletin	RSV	(Nothias-Scaglia et al. 2014)
61	*Euphorbia amygdaloides spp.* and *semiperfoliata*	Compound 3	CHIKV HIV-1 HIV-2	(Kapoor et al. 2017)
62	*Glycyrrhiza radix*	Glycyrrhizic acid	EBV	(Kapoor et al. 2017)
63	*Houttuynia cordata*	Quercetin 3rhamnoside	Influenza virus	(Kapoor et al. 2017)
64	*Limonium sinense*	Samarangenin B	HSV-1	(Huang et al. 2014)
65	*Liriope platyphylla*	LPRP-Et-97543	HBV	(Kapoor et al. 2017)
66	*Melia azedarach* L	Tetranortriterpenoid 1-cinnamoyl-3, 11-dihydroxymeliacarpin	VSV HSV-1	(Kapoor et al. 2017)
67	*Prunella vulgaris*	Lignin–carbohydrate complex	HSV-1 HSV-2	(Kapoor et al. 2017)
68	*Pterocarya stenoptera*	Pterocarnin A	HSV-2	(Wahyuni et al. 2014)
69	*Ruta angustifolia*	Chalepin and pseudane IX	HCV	(Cui et al. 2014)
70	*Saururus chinensis*	Manassantin B	EBV	(Li et al. 2005)
71	*Schefflera heptaphylla*	Dicaffeoylquinic acids	RSV	(Kapoor et al. 2017)
72	*Scoparia dulcis* L	Scopadulcic acid B	HSV-1	(Kapoor et al. 2017)

Table 1 (continued)

Sl. No	Plant name	Phytoactive compound	Effective against	Reference
73	*Scutellaria baicalensis*	5,7,4′ trihydroxy-8- methoxy-flavone	Influenza virus	(Qin et al. 2011)
74	*Tanacetum vulgare*	Spiroketalenol ether derivative	HSV-1 HSV-2	(Bauer and Brönstrup 2014)
75	*Veratrum sabadilla*	Sabadinine	SARS-CoV 3CL Protease	(Toney et al. 2004)
76	*Isatis indigotica*	Sinigrin	SARS-CoV 3CL Protease	(Lin et al. 2015)
	Chinese medicinal plants including *a. Forsythiae fructus* *b. Mori cortex* *c. Mori follum* *d. Chrysanthemi flos* *e. Farfarae flos* *f. Lonicerae japonicae flos* *g. Peucedani radix* *h. Rhizoma fagopyri cymosi* *i. Tamaricis cacumen* *j. Erigeron breviscapus* *k. Radix bupleuri* *l. Coptidis rhizome* *m. Houttuyniae herba*	Betulinic acid Coumaroyltyramine Cryptotanshinone Desmethoxyreserpine Dihomo-c-linolenic Dihydrotanshinone Kaempferol Lignan Moupinamide N-cis-feruloyltyramine Quercetin Sugiol Tanshinone IIa	SARS-CoV-2	(Zhang et al. 2020)

a broad-spectrum antiviral activity. Among these, *Lycoris radiate* (Li et al. 2005; Mani et al. 2020) and *Nigella sativa* (Idrees et al. 2021) had shown powerful anti-severe acute respiratory syndrome-related coronavirus (SARS-CoV or SARSr-CoV) activity. Several plant-derived phytoactive compounds previously known to have broad-spectrum antiviral effects could unveil new drugs for newly emerging novel viral strains (Table 1) (Fig. 2). Lycorine from *L. radiate* had shown a high efficiency against SARS-CoV (EC50 of 15.7 ± 1.2 nM), with more than 900 selectivity index. In this context, *L. radiate* has toxic effects at low levels (Kretzing et al. 2011; Mani et al. 2020). Theaflavin a phytoactive compound found in *Camellia sinensis* had been shown in silico effectively against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strains (Lung et al. 2020; Mani et al. 2020). The phytoactive compounds from all these above plants could be screened for SARS-CoV-2.

Phytoactive compounds for influenza

Influenza is the upper respiratory tract disease, involving seasonal or climatic occurrences from avian and other zoonotic origins, causing global 3 to 5 million morbid cases annually (Krammer et al. 2018). Previous and recent research shows a wide range of phytochemicals could prevent the influenza virus both in vitro (Eggers et al. 2022; Yang et al. 2022; Idriss et al. 2023a, b; Mothana et al. 2006; Pantev et al. 2006; Prajoubklang et al. 2005) and in vivo (Ivanova et al. 2005; Prahoveanu et al.

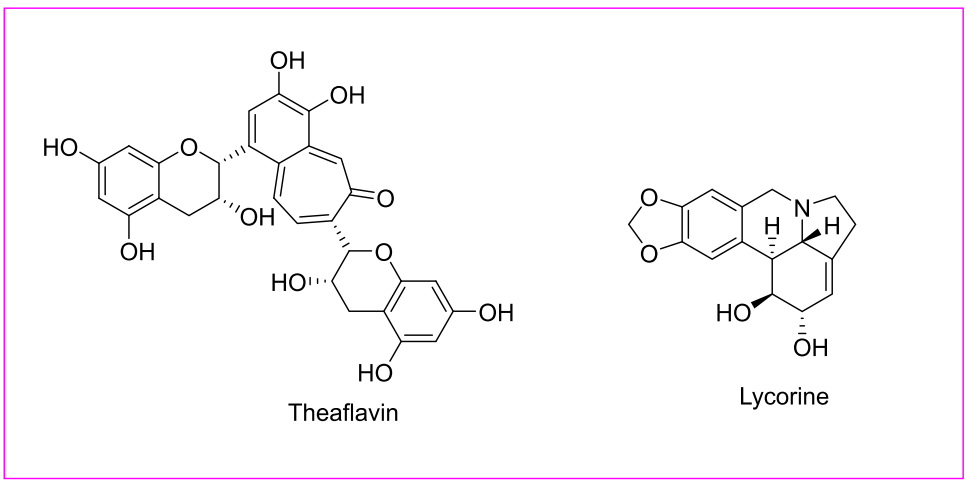


Fig. 2 Structure of the phytoactive derivative for emerging viral infectious diseases

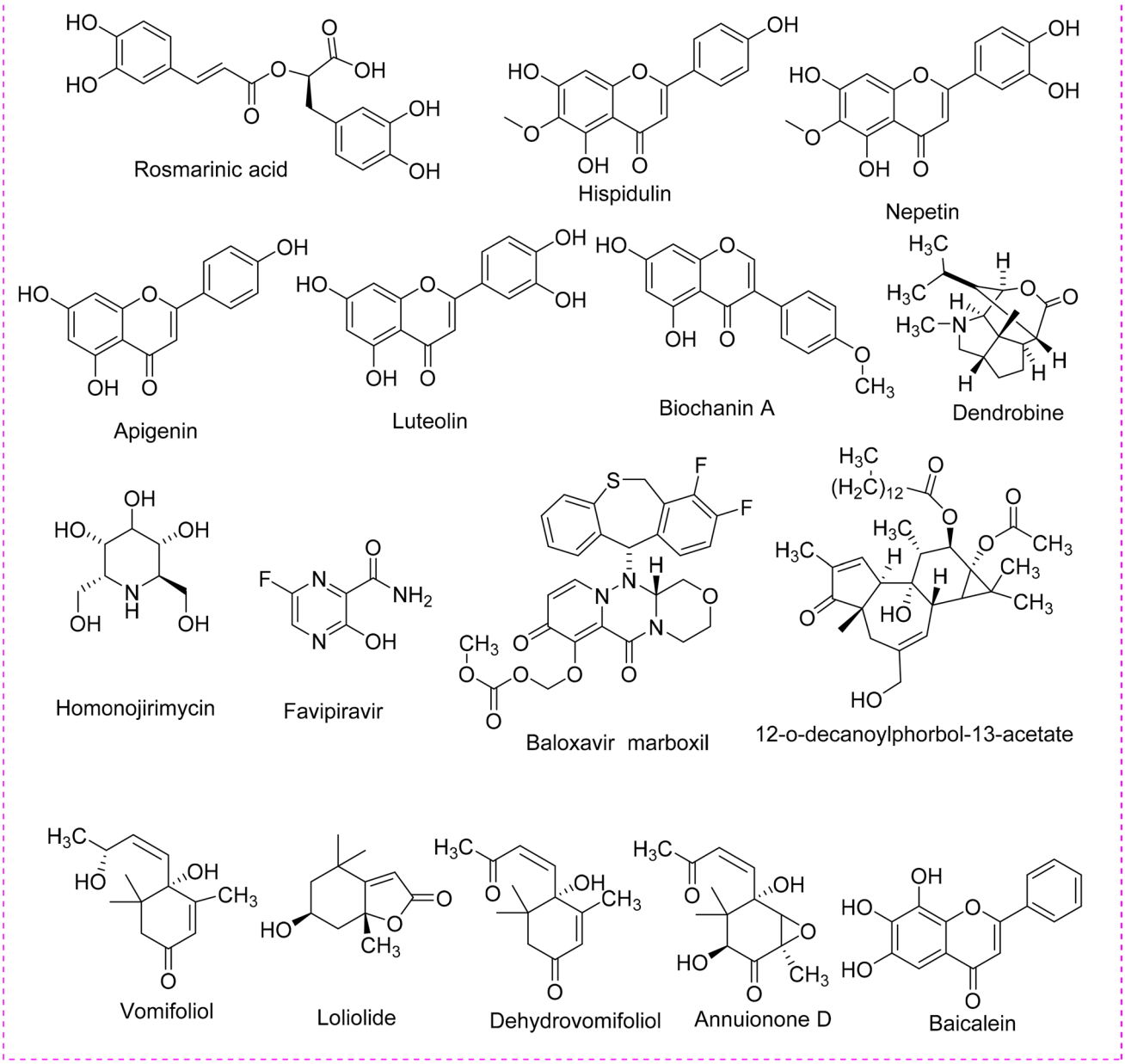


Fig. 3 **A** Reported active compounds for inhibitory action against influenza viruses. **B** Structure of Adamantane derivative for inhibitory action against anti-influenza. **C** Structure of the sialic acid derivative for inhibitory action against anti-influenza

1985). Moreover, flavonoids derived from aerial parts of *Salvia plebeia* were proven effective against influenza A (H1N1) neuraminidase, inhibiting the replication cycle (Bang et al. 2016). An alkaloid extracted from *Commelina communis*, the homonojirimycin (HNJ), had been reported to have strong anti-H1N1 activity in vivo and good survival rates in infected mice (Ghildiyal et al. 2020; Zhang et al. 2013). Investigations were shown as the potential anti-influenza activity by several phytochemicals (Table 1) (Fig. 3A–C), such as saponins, polyphenols, glucosides, flavonoids, and alkaloids (Cock and Vuuren 2020; Wang et al. 2006). This phytochemical would be capable of producing possible phytoactive compounds to control the influenza virus in the future.

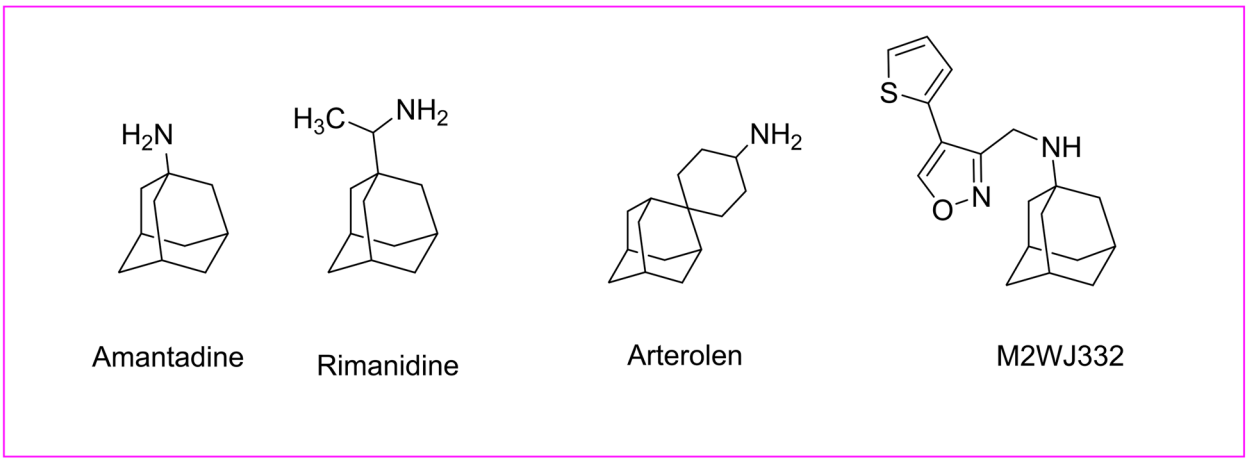
Role of phytoactive compound for HIV/AIDS

Human immunodeficiency virus (HIV) infects specifically $CD4^+$ T cells (helper T cells) weakening the immune system over the infection time, thereby causing the problem of acquired immunodeficiency syndrome (AIDS). Out of the

two main types of HIVs, HIV-1 is more potent and more contagious than HIV-2 and is the major cause of HIV contagion, worldwide. There are about 38 million people infected with HIV worldwide (WHO 2023). Recent literature suggested the use of phytoactive compounds could be affordable and proficient in inhibiting the HIV-1 progression (Table 1) (Fig. 4). These also ease toxicity issues of treatment, as phytochemicals do not accumulate significantly in human organs and can be easily digested and eliminated out of the body. The Canadian AIDS Treatment Information Exchange (CATIE) has summarized a list of potent medicinal plants with advantageous effects for HIV individuals. This list also provides identification and herbal products for controlling HIV and associated infections (Mukhtar et al. 2008). One such antiretroviral phytoactive compound could be derived from *Terminalia catappa*, *Jatropha curcas*, *Cordia spinescens*, *Hyptis lantanifolia*, and *Etrapteris macrocarpa* possessing anti-HIV properties (Matsuse et al. 1998). These are flavonoids cyanidin, ellagitannins, gallotannins, and tannins (Dwevedi et al. 2016). Griffithsin a lectin derived from *Griffithsia* sp., a red alga that inhibited the viral entry into the host cell. Similarly, cyanovirin-N derived from several cyanobacteria showed comparable inhibition of HIV entry. Mirabamide A and neamphamide A extracted from different sponges show anti-HIV activity even in low concentrations. Triterpene betulinic acid derivative bevirimat derived from Chinese traditional herbs have been shown in vitro to inhibit HIV with enhancing efficacy.

Phytoactive compound for herpesvirus

Human herpes viruses (HHVs) family has several varieties of DNA viruses, out of which herpes simplex virus 1 and 2 (HSV-1, HSV-2) cause the majority of infection. Other notorious HHVs, which cause infection are HHV-3, HHV-4, HHV-5, HHV-6A, HHV-6B, HHV-7, and HHV-8. Aqueous extract of *Podophyllum peltatum* L. prohibits



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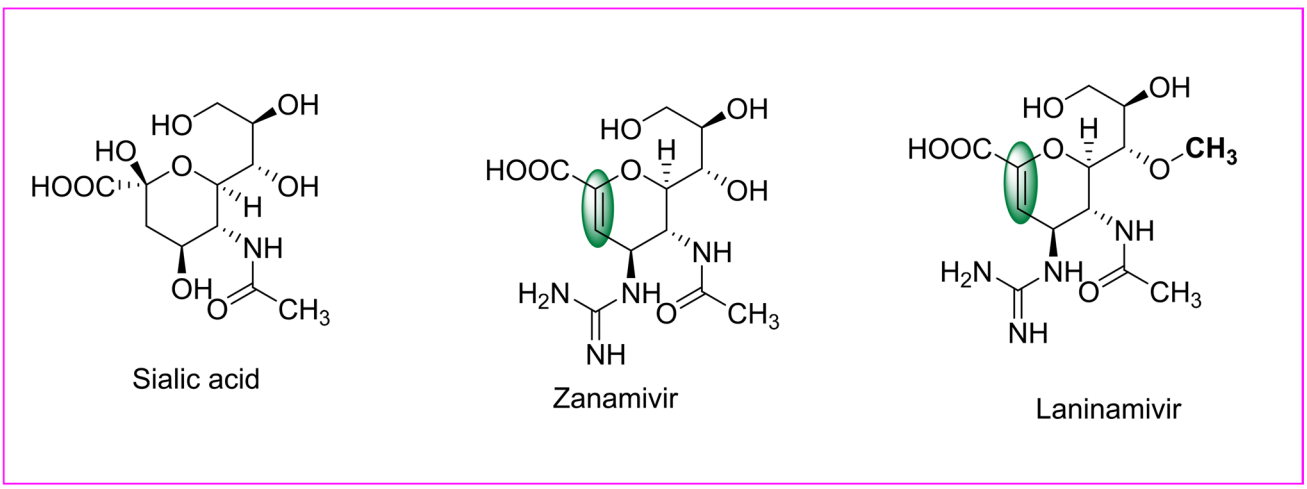

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Fig. 3 (continued)

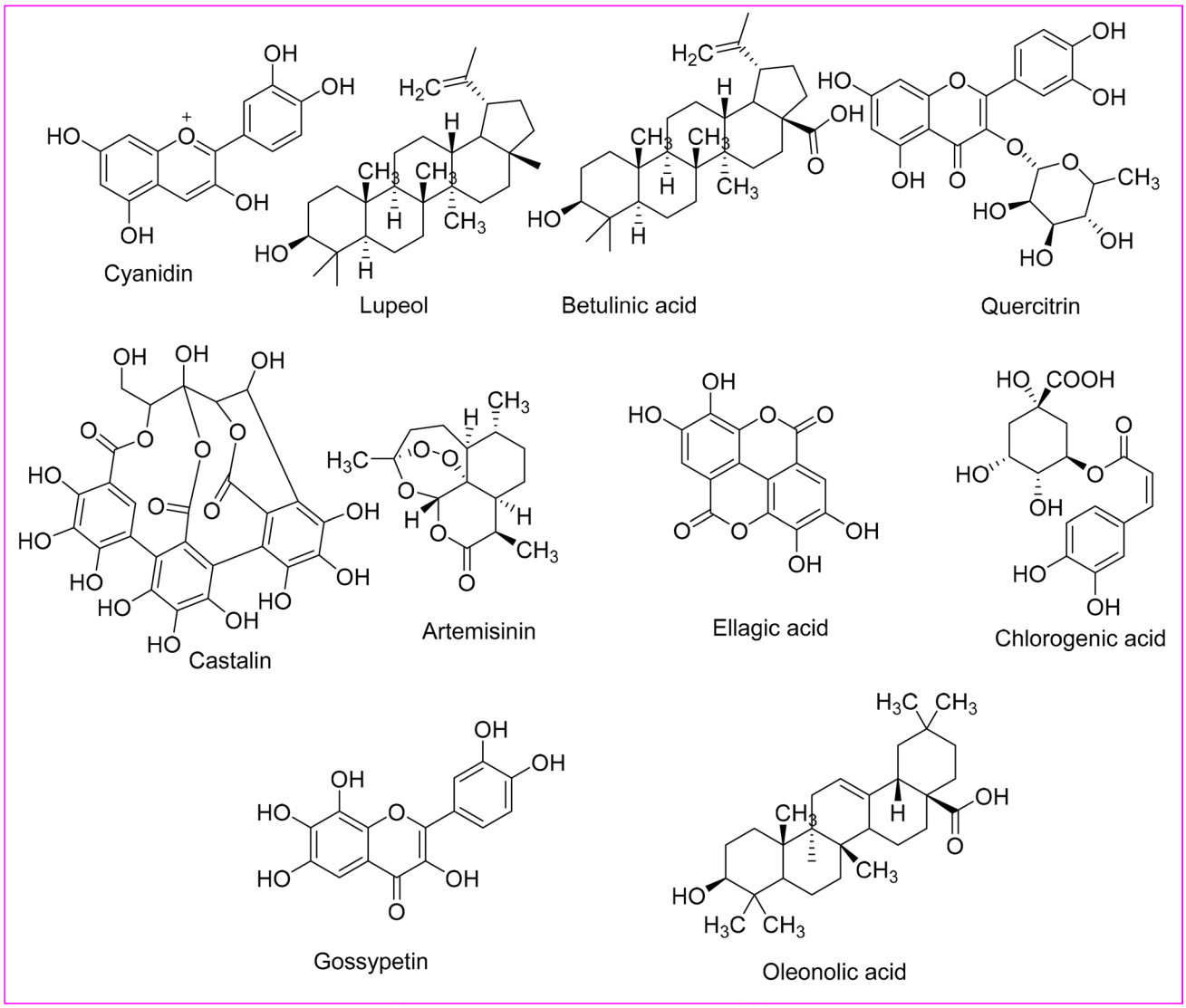


Fig. 4 Structure of the phytoactive compounds for HIV/AIDS

HSV-1 in vitro (Bedows and Hatfield 1982). Acetone extract of *Phyllanthus urinaria* and *Phyllanthus emblica* L. (Euphorbiaceae) could also inhibit HSV-2 and HSV-1 (Xiang et al. 2011; Yang et al. 2007a, b). Even extract of few other medicinal plants is effective, which suggest that phytoactive compounds have potential anti-HSV activity (Table 1) (Fig. 5). There is always a pursuit for anti-viral drugs, which could vanquish virus-resistant or repress the emergence of resistance viral strains. One such example is the roots of *Carissa edulis* Vahl (Apocynaceae) also showed a significant anti-HSV activity in vitro and in vivo (Mukhtar et al. 2008; Tolo et al. 2006). In recent studies, extract of *Ginkgo biloba* had been shown with potential anti-HSV activities suggesting *G. biloba* could supplement current therapies for HSV (Sochocka et al. 2019).

Phytoactive compound for hepatitis

Hepatitis is an inflammatory state of the liver that can provoke an array of health disorders and can be lethal. The five main strains of the hepatitis virus are type A, B, C, D, and E. However, types B and C are the most fatal, as those cause chronic diseases such as cirrhosis of the liver, cancer, and ultimately mortality (Roumy et al. 2020). Approximately 325 million people are living with hepatitis B and/or C worldwide by WHO, 2023. Clinical studies on different species of *Phyllanthus* sp. have revealed its anti-hepatitis B virus (HBV) properties, which inhibit HBV polymerase activity and mRNA transcription (Ravikumar et al. 2011; Lee et al. 1996; Ott et al. 1997; Wang et al. 2006). *Oenanthe javanica* (Apiaceae) had been shown as a

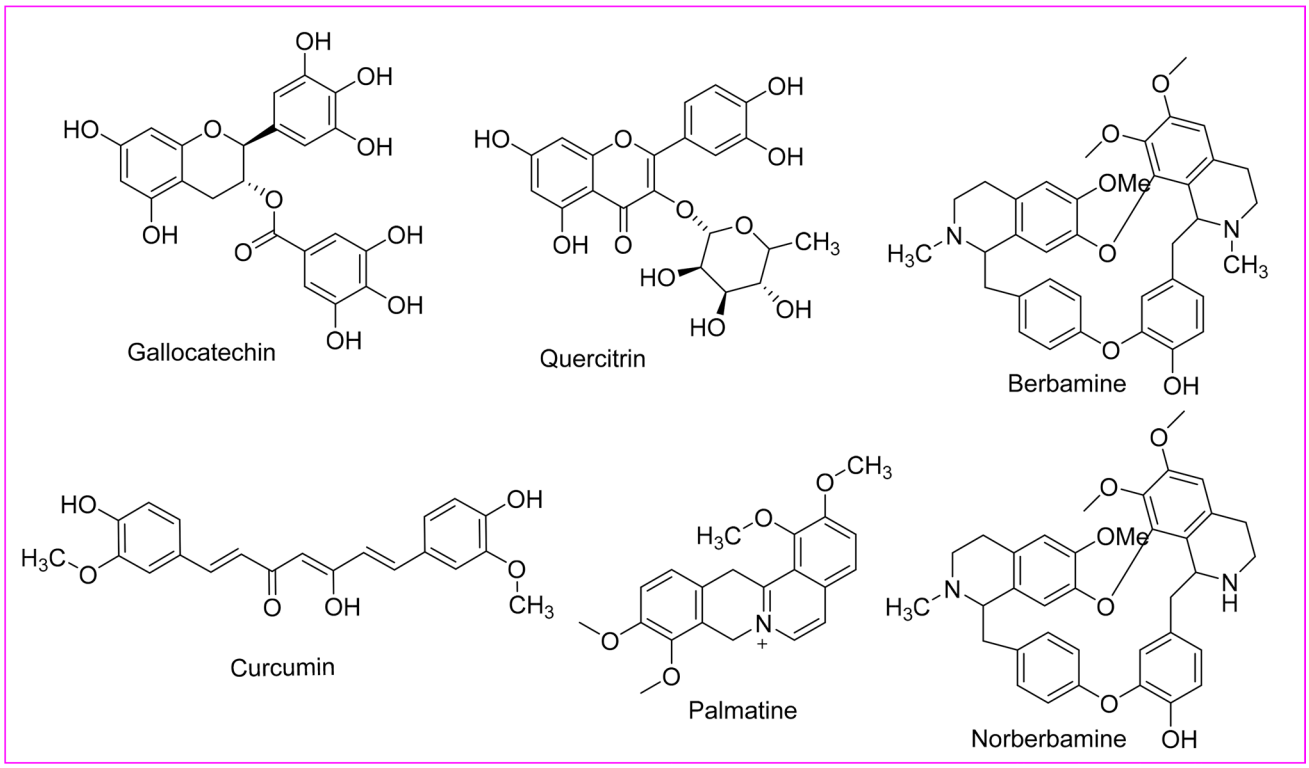


Fig. 5 Structure of the phytoactive compounds against herpes virus

potent inhibitor of hepatitis B e-antigen (HBeAg) and hepatitis B surface antigen (HBsAg) (Wang et al. 2005). Similarly, *Gymnema sylvestre* R. Br. (Apocynaceae) inhibited HBsAgs binding, with the additional inhibition of HBV DNA polymerase (Siddiqui et al. 2017). *Acanthus ilicifolius* L. (Acantheceae) lowered transaminase by reducing HBV-prompted liver damages (Siddiqui et al. 2017; Wei et al. 2015). Sometimes, combinations of extracts of different medicinal plants were tried for better effects in particular therapies. One such example was the combination of phytoactive compounds of the reishi mushroom, *Ganoderma lucidum* and *Sophorae flavescentis* (Fabaceae), which proved to have a powerful anti-HBV effect in vitro and in vivo (Li et al. 2005) (Table 1) (Fig. 6).

Phytoactive compound for chikungunya

Chikungunya virus (CHIKV) is causing surging "ignored" tropical infectious Arbovirus disease that causes a high fever and intense pain in joints (Arthralgia). It was first reported in 1952, and approximately, it has infected over 2 million people since 2005 by WHO, 2023. It has no specific anti-viral treatment, but the focus has been to relieve the symptoms. Diterpenoid type "trigowiin A" extracted from *Trigonostemon howii* (Euphorbiaceae) exhibited a moderate anti-CHIKV activity, and another unique indigenous plant *Trigonostemon cherrieri* (Euphorbiaceae) had a moderate to fair anti-CHIKV control (Bhakat and Soliman 2015). However, phytoactive compounds extracted from *Croton mauritianus* (Euphorbiaceae) leaves had some promising anti-chikungunya effects (Corlay et al. 2014). A coumarin derived from *Mammea americana* (Calophyllaceae) and *Tabernaemontana cymosa* (Apocynaceae) showed 100% inhibition for both chikungunya and dengue virus (Gómez-Calderón et al. 2017). Hexane extract of *Santalum album* (Santalaceae), *Trichosanthes dioica* (Cucurbitaceae), *Chrysopogon zizanioides* (Poaceae), and *Andrographis paniculata* (Acantheceae) contains coumarins, which is potential in inhibiting viral growth (Table 1) (Fig. 7). Therefore, these are mostly used for the treatment of both the chikungunya and dengue viruses (Ghildiyal et al. 2020).

Phytoactive compound for dengue

Dengue virus (DENV) has emerged as one of the virulent tropical and subtropical infectious arbovirus causing a disease, which causes a wide range of diseases ranging from subclinical disease to acute flu-like signs. It was first recorded during the 1950s, and now, approximately 100–400

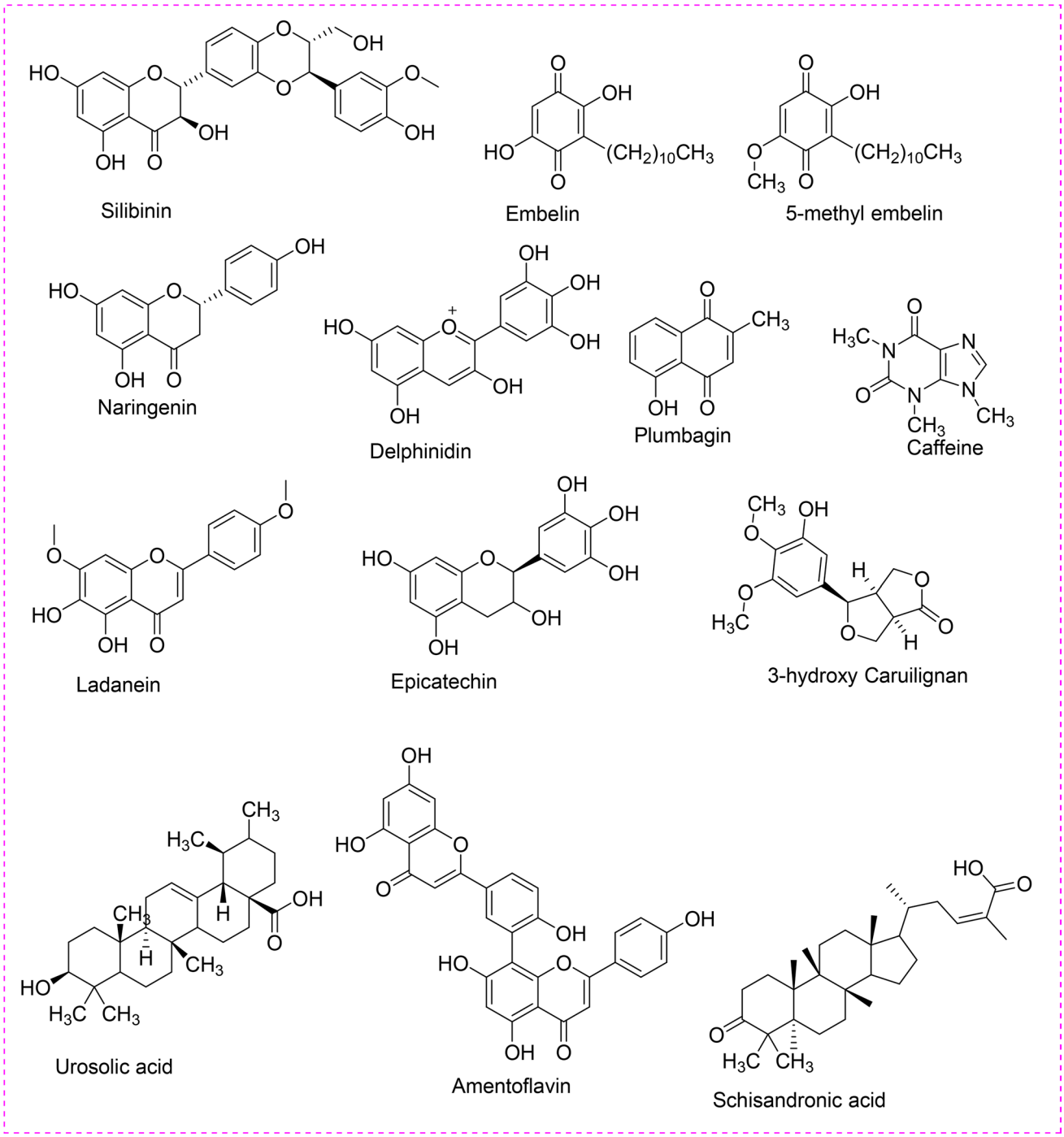


Fig. 6 Structure of the phytoactive compounds against hepatitis

million people are infected each year by WHO, 2023. It has no specific anti-viral treatment, but the focus has been to reduce fever and pain along with maintenance of the infected person's body fluid volume. It has four serotypes, meaning a person can be infected four times. An Ayurvedic poly-herbal concoction called Nilavembu Kudineer (NVK) with *Andrographis paniculata* as the main constituent and other extracts from *Mollugo cerviana* (Molluginaceae), *Piper nigrum* (Piperaceae), *Zingeber officinale* (Zingeberaceae), *Cyperus rotandus* (Cyperaceae), *Trichosanthes cucumerina*, *Santalum album*, *Vetiveria zizanioides* (Piperaceae), and *V. zizanioides Hedyotis diffusa and Artemisia capillaris* had been reported to show good anti-DENV and anti-CHIKV during infection in vitro (Mao et al. 2022; Jain et al. 2020).

Baicalein and fisetin phytoactive compounds had been shown to impede replication at different stages. Furthermore, flavonoids obtained from *Tephrosia madrensis* (Cucurbitaceae), *T. viridiflora*, and *T. crassifolia* showed a 70% inhibition on dengue viruses (Sánchez et al. 2000). Acetone-soluble leaf extract of *Pavetta tomentosa* (Rubiaceae) and *Tarenna asiatica* (Rubiaceae) had also been recently reported for the potential anti-dengue effects (Pratheeba et al. 2019) (Table 1) (Fig. 8).

Phytoactive compound for Zika

Zika virus (ZIKV) is another resurging tropical infectious, Arbovirus disease causes mild fever, malaise conjunctivitis, rash, and joint and muscle pain. This also increased the risk of neurologic disorders such as myelitis, neuropathy, and the Guillain-Barré syndrome. It was first reported in monkeys in 1947 and thereafter in humans in 1952 in Uganda. It can also be transmitted through sexual contact, organ transplantation, from mother to fetus during pregnancy, and transfusion of blood and blood products by WHO, 2023. It has no specific anti-viral treatment, but in recent years, researchers have detected curcumin and pinocembrin found in turmeric, and tea extracts from *Hedyotis diffusa* and *Artemisia capillaris* are found to have replication repressive effect (Mao et al. 2022), respectively in having anti-ZIKV effects (Akbar et al. 2018; Lee et al. 2019). Extract from endemic plants, *Aphloia theiformis* (Aphloiceae) and *Psiloxylon mauritianum* (Myrtaceae), found at Reunion Island, inhibited ZIKV adherence to cell surface makings by both anti-ZIKV and anti-DENV (Clain et al. 2019, 2018). Hexane extracts of *Tontelea micrantha* (Celastraceae) were also reported to have a promising result of anti-ZIKA effect with no cytotoxicity in vitro (Ferreira et al. 2019) (Table 1) (Fig. 9).

Phytoactive compound for Ebola

Ebola virus disease (EVD) is a rare but severe, often fatal resurging infectious disease, which causes the hemorrhagic fever. It was first reported in 1976, and in the recent 2018–2019 outbreak, it caused an average fatality rate of about 50%. It can be transmitted from human to human by blood or body fluids by WHO, 2023. As there is no proven treatment, only supportive care and experimental Ebola vaccine have improved the survival rate. WHO and Centers for Disease Control and Prevention (CDC) have estimated rate t as label 4 virus (requiring biosafety level

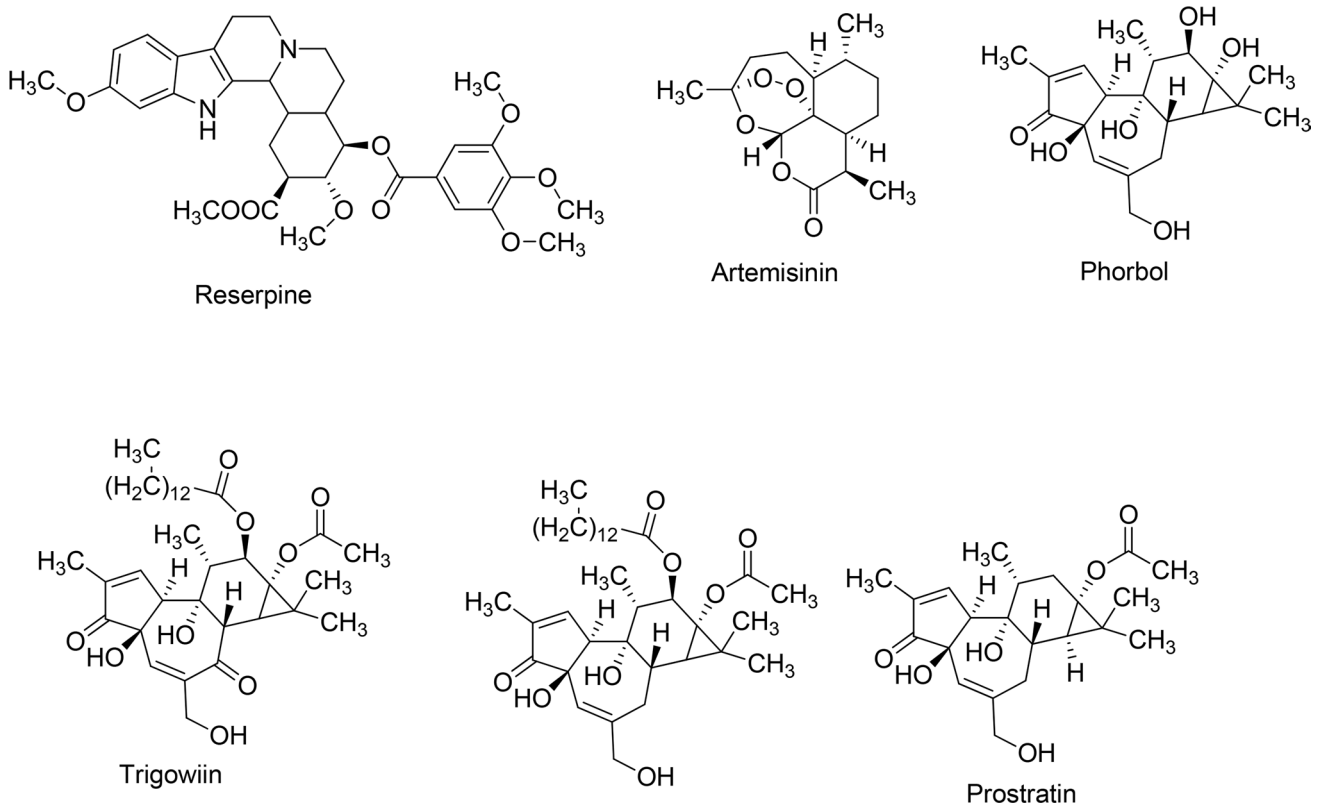
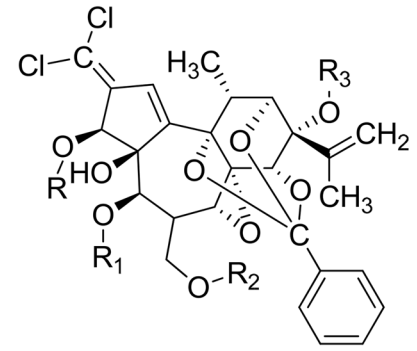
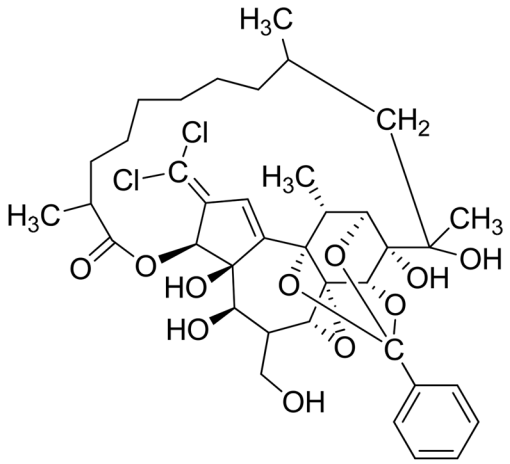


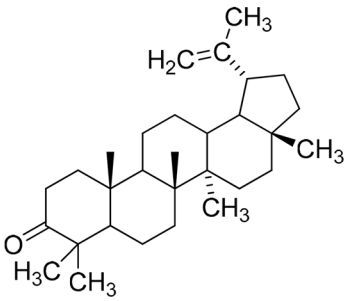
Fig. 7 Structure of the phytoactive compounds for chikungunya



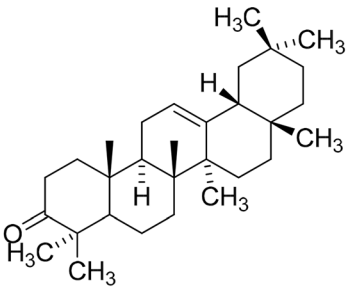
Trigocherrin A ; R=Bz, R_1=R_2=$COCH_3$, R_3=H
Trigocherrin B ; R= R_1=H, R_2= R_3=Bz
Trigocherrin C; R=R_3=Bz, R_2=R_3=Bz



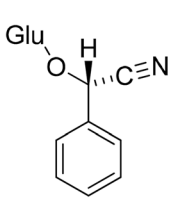
Trigocherriolides



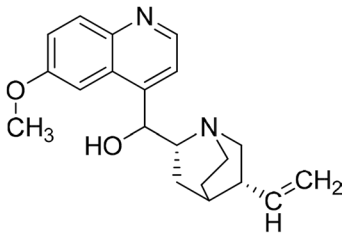
Lupenone



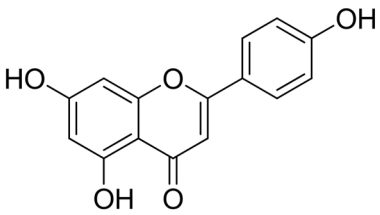
Beta amyrone



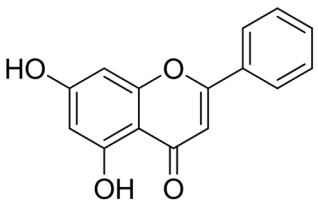
Sambunigrin



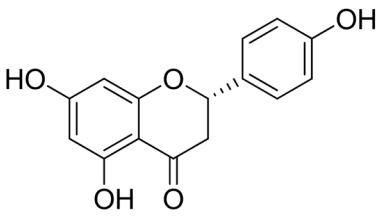
Quinine



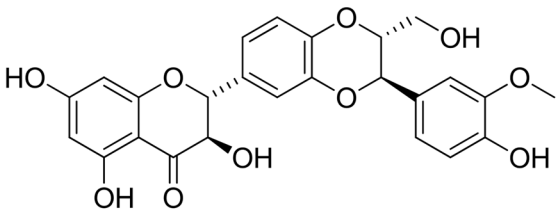
Apigenin



Chrysin



Naringenin



Silibinin

Fig. 7 (continued)

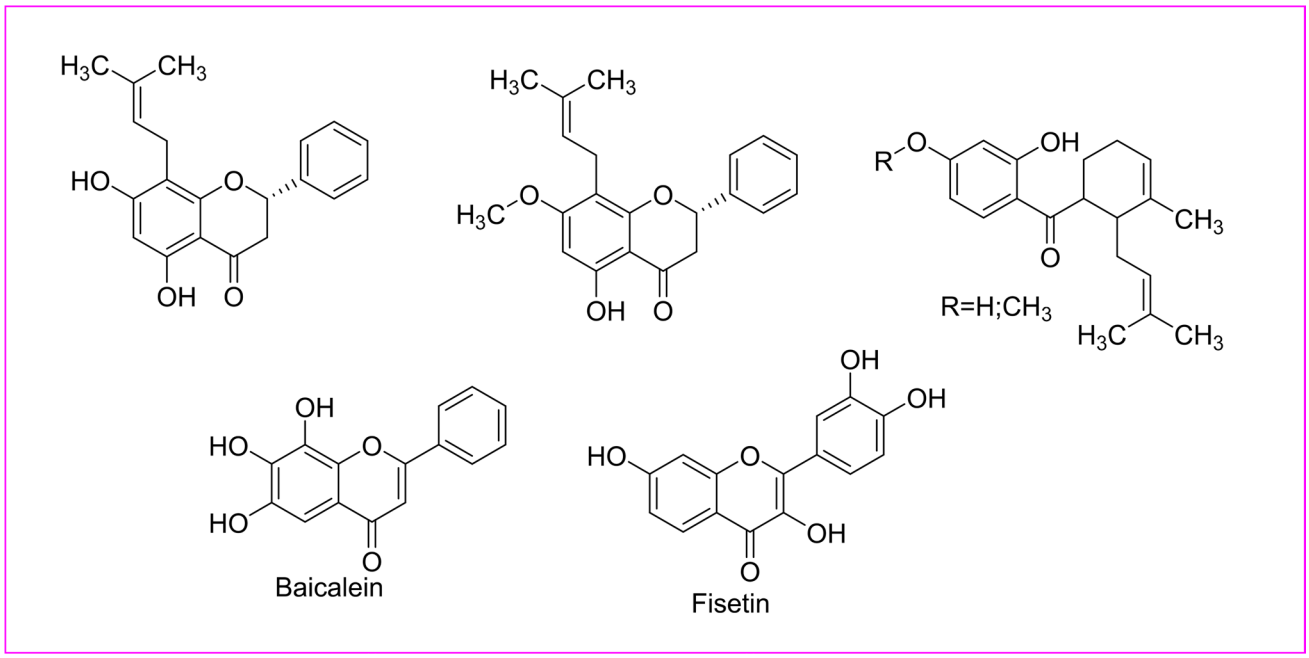


Fig. 8 Structure of the phytoactive compounds for dengue

4-equivalent containment) by CDC, 2009. Leaf and bark extracts of *Aglaia foveolata* (fam. Mahogany) and aqueous extracts of *Prunella vulgaris* (Lamiaceae) had shown to have an anti-EVD effect (Ben-Shabat et al. 2020; Kapoor et al. 2017). In silico-based drug design had shown bioactive compounds extracted from *Andrographis paniculata* (Acanthaceae), *Fumaria indica* (Papaveraceae), and *Adhatoda vasica* (Acanthaceae) which had shown the best docking conformations of the ligands against Ebola virus (EBOV)-glycoprotein-and-host-cell-proteins, suggesting a possible anti-EVD from these plants (Shaikh et al. 2019). Curcumin found in turmeric had proven to be effective anti-EBOV (Baikerikar 2017) (Table 1) (Fig. 10).

Phytoactive compound for Marburg

Marburg virus disease (MVD) is a rare but highly virulent infectious disease that causes hemorrhagic fever with a fatality rate of 88%. Its Ebola virus belongs to the Filoviridae family of viruses and was first reported in 1967. Both the diseases are clinically similar and highly potent to cause histrionic outbreaks with high casualty rates by WHO, 2023. It had been declared as label 4 virus by WHO and CDC in 2009. The in silico-based drug design had shown bioactive compounds extracted from *Murraya koenigii* (Rutaceae) leaf had shown the best docking confirmations for 6 proteins of Marburg virus (MARV) (Taj et al. 2018). Bioactive

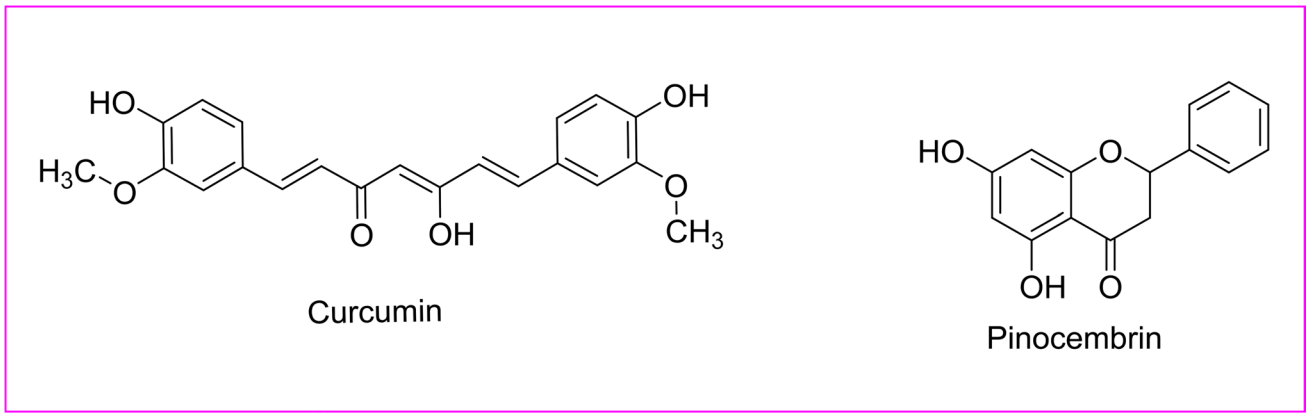
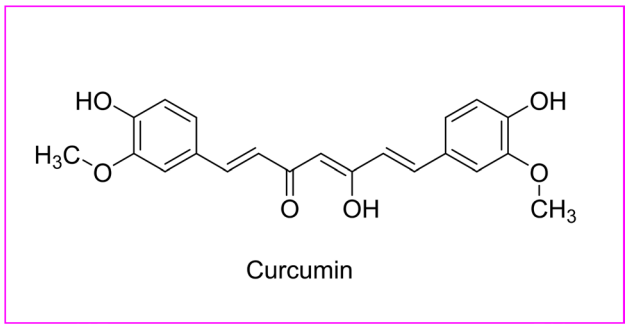


Fig. 9 Structure of the phytoactive compounds for Zika



Curcumin

Fig. 10 Structure of the active compounds for Ebola

compounds such as palmatine, squalene chloride, delphinidin, and marmin show the maximum binding energy for MARV protein in silico (Badoni et al. 2015) (Fig. 11).

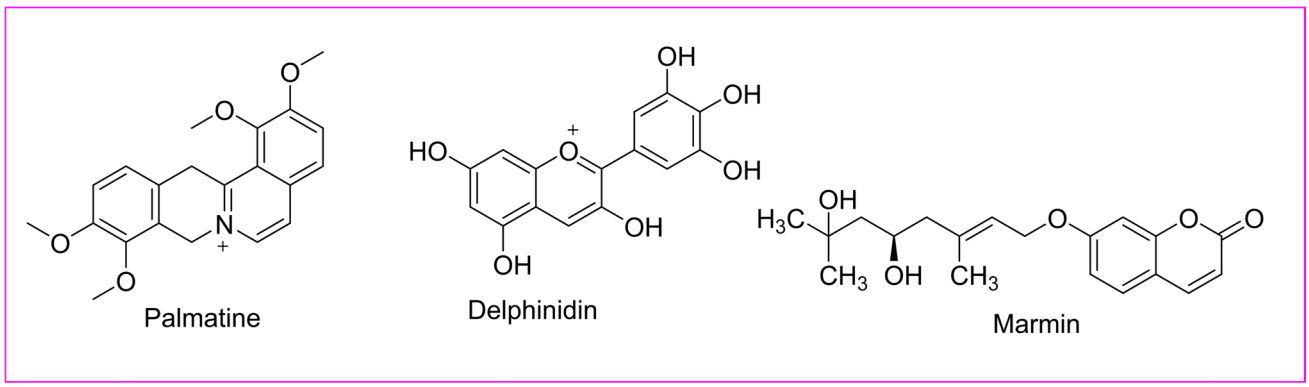
Mechanism of action and effect of anti-viral phytoactive compounds

Viruses contain a genome (DNA or RNA) covered by a protein capsule, which stores a few enzymes and in some may be covered by a lipid envelope. The main concept behind the anti-viral drug is to recognize viral proteins or parts of viral proteins, that can be deactivated/weakened/destroyed, obstructing viral replication by inhibiting the entry of the virus into the host cell in controlling the viral uptake, attaching to surface receptors, and by competing for pathways of activation of intracellular signals (Ghosh et al. 2009; Kapoor et al. 2017; Khan et al. 2005; Mohapatra and Dar 2010). For a drug to have the broad-spectrum effect, the viral targets should also be common for many strains of a virus or at least, for different species in the same family. Creating secure and potent anti-viral drugs is tough, as viruses tend to replicate in a host cell (hard to find viral targets without damaging host cell), mutate fast, viral variation, and in the long term develop resistance. Each virus has a specific life cycle depending on the strain, but those all follow a specific pattern: (1) adhesion to host cell, (2) liberation of the viral genome and perhaps enzymes into the host cell, (3) replication of viral parts by subjugating host-cell machinery, (4) congregation of viral parts into full viral particles, and (5) liberation of viral particles to infect fresh host cells (Fig. 12).

One of the strategies is to inhibit the adhesion of the virus to the host cell. This would be achieved by blocking receptor sites on host cells by anti-virus-associated protein (VAP) antibodies. Inhibiting the entry by a powerful entry-inhibitor or entry-blocker agent may not only impede the spreading of the virus within an infected person but also the dissemination from an infected person to an uninfected person is stopped. Eventually, this will result in difficulties for the virus to develop resistance, as those would not use host-cell machinery to reproduce and mutate. Even research has been conducted for blocking sockets on the viral surface that checks the un-coating process. The next strategy is to focus on methods virus use to synthesize Alarcón by subjugating host-cell machinery. The target is to block at the label of transcription, translation, and post-translational modifications (Alarcón et al. 1988; Deas et al. 2005; Ryu and Lee 2003). Thereafter, the next step is to inhibit the congregation of viral parts into full viral particles and releases (Sodeik et al. 1994). The final and important step is to stimulate the immune system to attack viruses by generating antibodies and interferon (Samuel 2001) (Fig. 12).

Structural activity relationship studies of antiviral action of phytocompounds

Many flavonoids including baicalein, fisetin, quercetin, and naringenin had been used to control the replication of several viruses from which, baicalein deteriorated the structure of the Japanese encephalitis virus (JSV) and interfered the viral absorption, but quercetin had no other



Palmatine Delphinidin Marmin

Fig. 11 Structure of the active compounds for Marburg

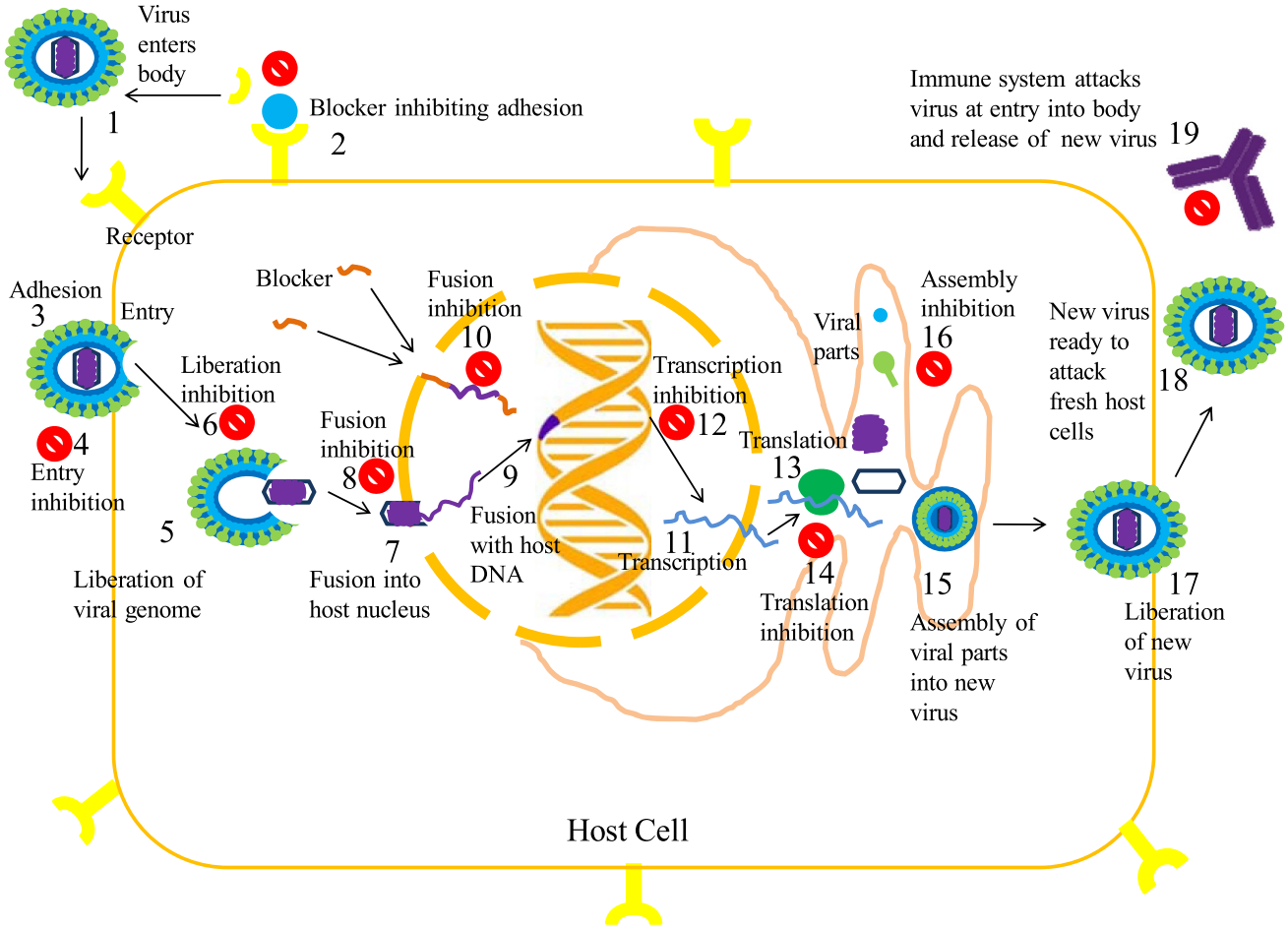


Fig. 12 Schematic representation of the mechanism of action and effect of anti-viral phytoactive compounds through virus life cycle

antiviral action with JSV. As per the structural concerning of these flavonoids, quercetin, fisetin, and kaempferol, the latter is chemically a flavonol (3-hydroxy flavone) derivative, whereas baicalein had the flavone structure that makes it less polar than flavonol derived glycosides. The flavonoids with less hydrophilic give more response against JSV. Similarly, the flavylium salt dalphinidin had shown having more binding affinity with a MARV protein that was proven by a molecular docking study. Flavanone-derived glycoside, naringenin, had been a potent antiviral with action against dengue fever. Chemically, α-β unsaturated β-diketone, aromatic methoxy, and the phenolic system in the curcumin structure are responsible for antiviral action against Ebola and Zika viruses. The diketone system of curcumin was converted into enolates that were readily deprotonated and acted as an acceptor in Michael's nucleophilic addition reaction. For the enhancing of the aqueous solubility of curcumin, the chemical modification of α-β unsaturated β-diketone moiety led to producing a potent antiviral candidate. The presence of endoperoxide, a lactone group in artemisinin structure, and their semisynthetic derivatives might be responsible for a good antiviral action against the chickenguniya virus. Additionally, the trigocherrin A (dechlorinated methylene diterpene orthoester) had exhibited a potent and selective effect against the chikungunya virus in Vero cells. Overall, concisely, for the essential structural activity study of phyto-oils for the inhibition of different viruses, the presence of polyphenolic moiety in coumarin or chromone fused ring system, dihydrochalcone group, lactone derived endoperoxide group, or pentacyclic triterpenoid saponin within the ring system containing benzoquinone ring and gallate of catechin must be helpful.

Conclusions and future perspectives

In the realm of targeted therapies, there is a necessity for some low-cost, potent, and safe anti-viral drugs/therapies with the least side effects. Therefore, the suitable phytoactive compound(s) can be effective in developing such anti-virals,

as selective non-toxic plant products would be metabolized and excreted without increasing any cell toxicity. Collaborative work can be done in the future by combining new as, the reported anti-viral phytoactive compounds with already approved drugs for enhanced and durable effectiveness. Phytochemicals can be converted to nanosuspensions, nanoparticles, nanocapsules, microspheres, solid dispersions, crystals, micelles, self-nanoemulsifying and self-microemulsifying drug delivery systems (SNEDDS and SMEDDS), for improved targeted delivery, extended activity, and superior effects, as seen against in "Mainstream medicines." Moreover, every country should encourage exclusive research to explore in and around various biodiversity-rich zones and contact ethnomedicine practitioners to identify more potential phytoactive compounds with anti-viral effects, for the global issues of viral diseases.

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Author contribution SM, CRS: formal analysis, data curation, software, and validation. SM, CRS, SKP: writing of this manuscript and critical revision. RNP: edited the whole manuscript. All authors read and approved the final manuscript. The authors confirm that no paper mill and artificial intelligence was used.

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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