Chapter 4
Plant-Based Natural Products: Potential Anti-COVID-19 Agents

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Introduction

Viral infections are becoming common day to day and cause many chronic human diseases. Viruses are responsible for numerous chronic diseases and hard-to-cure syndromes like HIV, hepatocellular carcinoma, HCV, type 1 diabetes, Alzheimer's disease, etc. [1–3]. The current outbreaks of globalization, increased global travel, and drug-resistant viral strains have underscored the protection of human health: the emergence of coronavirus, dengue virus, severe acute respiratory syndrome (SARS) virus, measles virus, West Nile virus outbreaks, and influenza virus [4–6].

Despite the drug and vaccine advancement, there is still a need of novel antiviral drugs or vaccine therapies that are extremely efficacious as well as economical for the control and management of viral infections. Viral infection can be avoided by either minimizing the exposure to viruses, sanitizing the skin, or boosting the immunization, and mucosal surfaces would reduce the risk of infection. However, with such a great care, there is still a need of effective treatments by virucidal or antiviral agents. Natural products especially secondary metabolites are an excellent source as therapeutic agents. They have a great antiviral potential, so are used as herbal medicines and in various pharmaceutical products from many decades. According to the

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WHO report, 80% of the world's population depend upon the traditional plants (i.e., phytochemicals) to use as therapeutic agents [7].

Purified natural products and herbal medicines act either as a starting raw material or as an intermediate source for new antiviral drug development. Mechanisms of antiviral actions depicted by the natural agents have shed light on the site of binding or interaction with the viral life cycle, like viral entry, release, assembly, replication, and structure-activity relationship as well as targeting of virus host-specific interactions.

Antiviral Mechanistic Aspects of Phytochemicals

The phytochemicals were studied for their antiviral potential for more than six decades. There are a number of action mechanisms attributed to their antiviral activity, as explained in Table 4.1. The basic advantage of these plant-derived products is their nontoxicity with no or less side effects to human body as compared to the synthetic antiviral drugs. The structure-activity relationship is developed to explain the antiviral effect of these compounds.

Mechanism

Natural phytochemicals bind either directly or indirectly to the virus cell during their virucidal activities and retard the virus growth. Basically, three modes of action mechanisms were identified antiviral reagents directly:

Virucidal effect, i.e., antiviral compounds, directly inactivates the viruses.
Antiviral compounds accelerate CPE on the virus-infected cells.
Antiviral compounds inhibit the few replication steps of the virus.

For example, octyl gallate showed its antiviral potential via following all these mechanisms against HSV-1. As it is ineffective against non-enveloped poliovirus, it requires lipid envelope for its virucidal activity. According to one study, its antioxidant property helps to inactivate non-enveloped virus, which may be somehow similar to the oxidation of lipids [8].

Plant Selection for Antiviral Screening

In plant selection for antiviral screening, four basic approaches must be considered:

Random plant collection followed by mass screening
Literature-based follow-up of the existing natural products

Table 4.1 Antiviral potential of many natural products against specific strains of viruses

Sr. no.	Name of the phytochemicals/extract from plants/class	Virus	Source	Details of the study	Mechanism	References
1.	Polyphenolic compounds (PC) containing: Flavonoids Catechins Monne Myricetin Quercetin Kaempferol Ramnasin Retusin			The effect of polyphenolic compounds was studied on the expression of viral proteins on the surface of virus-infected cells. The effect of viral proteins, i.e., nucleoprotein (NP), neuraminidase (NA), and hemagglutinin (HA) on the surface of infected cells was examined by ELISA (with monoclonal antibodies)	Total viral protein synthesis is inhibited by polyphenolic complex compounds, and the synthesis of hemagglutinin, neuraminidase, and nucleoprotein is also inhibited in the virus replication cycle	[9]
2.	Ent-epiafzelechin (4α→8)-epiafzelechin	Herpes simplex virus (HSV-2)	Extracted from *Cassia javanica*		Inhibits HSV-2 viral replication	[10]
3.	Excoecarianin	Herpes simplex virus (HSV)	Extracted from *Phyllanthus urinaria*		Inactivation of virus particles	[11]
4.	Chebulagic acid and punicalagin	Herpes simplex virus (HSV-1)	Derived from *Terminalia chebula* Retz.		Exhibits their antiviral potential as a GAG-competitor on the cell surface by inhibiting the viral entry (i.e., binding as well as fusion) and also by postinfection Cell-to-cell spread	[12]

(continued)

Table 4.1 (continued)

Sr. no.	Name of the phytochemicals/extract from plants/class	Virus	Source	Details of the study	Mechanism	References
5.	Meliacine	Herpes simplex virus (HSV-2)	Extracted from *Melia azedarach*	HSV-2 infection in a mouse model	Induces IFN-γ and TNF-α formation	[13]
6.	Quercetin (Q) 3-O-methylquercetin (3MQ) Luteolin (LU)	Herpes simplex virus (HSV-1)		Effect on the HSV-1 viral replication cycle	Interferes with the steps taking place between the 3 and 9 hours of replication cycle of HSV-1, i.e., transcription and translation of virus proteins	[14]
7.	Melittin	Human immunodeficiency virus (HIV-1)			Inactivates virus by disturbing the lipid envelope formation of virus	[15]
8.	Tricyclic coumarin	Human immunodeficiency virus (HIV-1)	Extracted from *Calophyllum brasiliense*		Inhibits viral replication in both chronic and acute infections by inactivation of NF-κB	[16]

Sr. no.	Name of the phytochemicals/extract from plants/class	Virus	Source	Details of the study	Mechanism	References
9.	Flavonoids complex: Amentoflavone Agathisflavone Baicalin Chrysosplenol C Coumarins Galangin (3,5,7-trihydroxyflavone) Glycosides Iridoids Morin Phenylpropanoid Rhusflavanone Robustaflavone Succedaneflavanone Theaflavin Quercetin Isoquercetin	Human immunodeficiency virus (HIV)		Effect on viral replication	HIV inhibitory activity was reported by blocking the RNA synthesis	[17–19]
10.	BCA, BA (flavonoid Baicalein)	HIV-1		Determining the action of mechanism of the antiviral effect of BA	BCA and BA (flavonoid Baicalein) both exhibited the *anti*-HIV-1 potential at the early stage of viral infection, i.e., at the time of viral entry into the host cell	[20]
10.	Extract from *Pelargonium sidoides*	Influenza virus	Isolated from *Pelargonium sidoides* roots		Inhibits viral entry and release, inhibits viral hemagglutination and neuraminidase (NA) activity	[21]

(continued)

Table 4.1 (continued)

Sr. no.	Name of the phytochemicals/extract from plants/class	Virus	Source	Details of the study	Mechanism	References
11.	Aqueous extract from dandelion	Influenza virus	Isolated from *Taraxacum officinale*		Inhibits the viral NP RNA levels and activity of polymerase	[22]
12.	Flavone (4′,5-dihydroxy 3,3′,7-trimethoxyflavone)	*Coxsackievirus* *Rhinovirus* *Picornavirus*		Show effects on viral replication	By selective inhibition RNA synthesis of virus in the cell culture as well as by inhibiting the virus replication	[23]
13.	Galangin 3-methyl ether Morin Quercetin Quercetin 7,4′-dimethyl ether Quercetin 3,7,3′4′-tetramethyl ether Quercetin 3,7,4′-trimethyl ether Quercetin 7-methyl ether Quercetin 3-methyl ether Robinin 7,4′-di-O-benzolquercetin 7-hydroxy-3,4′-dimethyl flavone 6,3′-dihydroxy-4′-methyl aurone Fisetin 4′-methyl ether	Tomato ringspot *Nepovirus* (TomRSV)		Effect on TomRSV infection in *Chenopodium quinoa*	Proposed that flavonoids delayed the early event in the virus life cycle, so there was a decreased titer and infectivity in tissue culture	[24]

Sr. no.	Name of the phytochemicals/extract from plants/class	Virus	Source	Details of the study	Mechanism	References
14.	Amentoflavone Quercetin Scutellarein	RAV-2 MMLV AMV		Study the effect on DNA synthesis	Inhibit reverse transcriptases (RT): RAV-2 RT MMLV RT AMV RT	[25]
15.	BCA, genistein	HCMV		Study of antiviral potential of genistein and baicalin against human cytomegalovirus	Proposed primary mechanism of baicalein was reported by blocking the HCMV entry into the host cell while for genistein by inhibiting the functioning of immediate-early protein 6 of HCMV	[26]

Ethnomedical approach
Chemotaxonomic approach [27]

The most preferred choices are the second and third ones, due to their cost-effective applicability. The folkloric created selection also demonstrated the five times more preferable therapeutic phytochemicals as compared to other approaches. Combining different section approaches like ethnomedical, taxonomical, and phytochemical methods collectively is also considered as the best choice. The random selection approach generally finds more novel antiviral natural compounds.

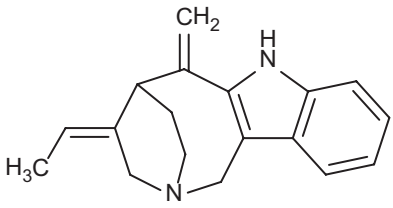
Different Classes of Phytochemicals as Antiviral Agents

Various classes of naturally occurring phytochemicals as antiviral agents are discussed in detail with reference to sources of origin, specificity, mechanistic action, structure-activity relationship (SAR), phase trials, etc.

Alkaloids

Alkaloids are a class of heterogeneous compounds having nitrogen atom linked with heterocyclic ring system. They possess basic character generally. Amino acids are usually the precursors for their biosynthesis within the plant body [28]. Handsome number of alkaloids showed potent antiviral activity. One of the studies on the 36 alkaloids isolated from *C. lanceus* or *Catharanthus roseus* as antiviral agents against polio type III and vaccinia viruses was reported. The results showed that the nine alkaloids were more potent as antiviral agents and pericalline was the most effective [29] (Fig. 4.1).

Another research group developed a structure-activity relationship (SAR) for chromone-based alkaloids, extracted from *Schumanniophyton magnificum* as anti-HSV and anti-HIV agents in Vero cells and C8166, respectively. The research group was synthesized their methyl and acyl analogs and developed their SAR. It was



Pericalline

Fig. 4.1 Structure of pericalline

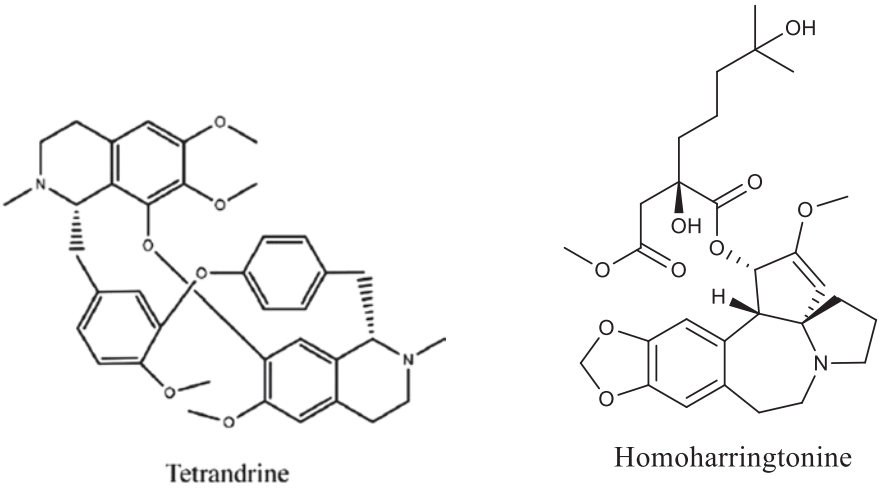


Fig. 4.2 Structures of tetrandrine and homoharringtonine

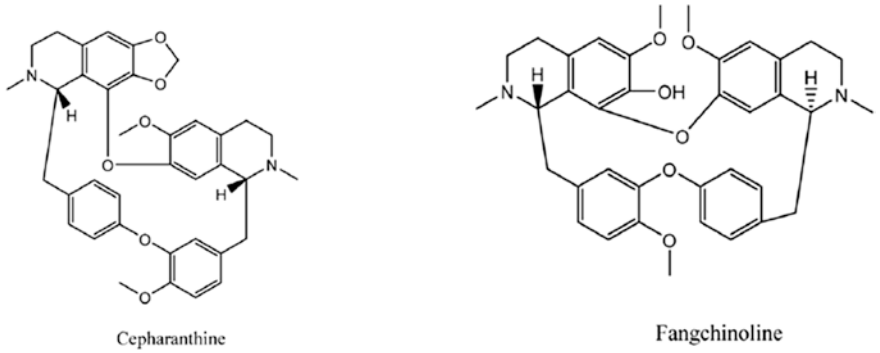


Fig. 4.3 Structures of cepharanthine and fangchinoline

concluded that the anti-HIV protentional is due to the presence of a free hydroxyl groups and piperidine ring [30] (Fig. 4.2).

Cepharanthine, an alkaloid, also showed remarkable antiviral potential by inhibiting the SARS-CoV protease enzyme at 0.5–10 μg/mL (Fig. 4.3) [31].

In another study, two alkaloids, i.e., 7-methoxycryptopleurine and tylophorine (Fig. 4.4), were isolated from *Tylophora indica* and tested for their inhibitory action for S and N protein activity, transmissible gastroenteritis virus, and enteropathogenic coronavirus replication [32]. These alkaloids showed excellent antiviral potential with IC_{50} values of <0.005 μM and 0.018 μM, respectively.

A recent research on berbamine showed its excellent antiviral activity against HCoV-NL63 with IC_{50} value 1.48 μM (Fig. 4.5).

Another research on antiviral potential of potent alkaloids, i.e., emetine, lycorine, and mycophenolate mofetil, against MERS-CoV, HCoV-NL63, HCoV-OC43,

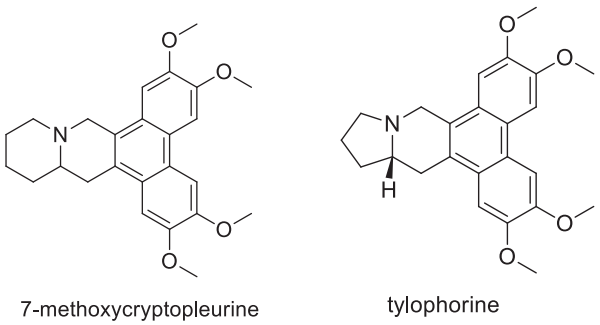


Fig. 4.4 Structures of 7-methoxycryptopleurine and tylophorine

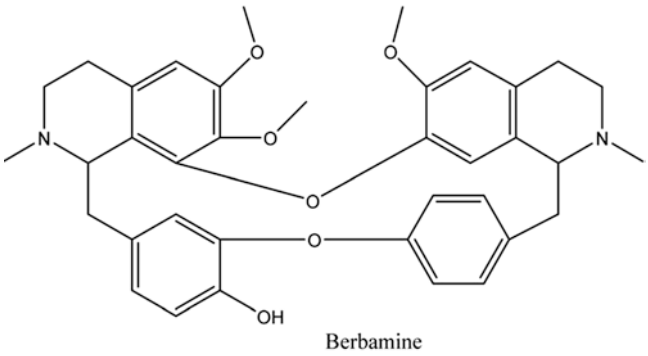
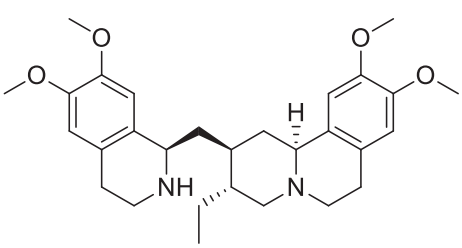


Fig. 4.5 Structure of berbamine

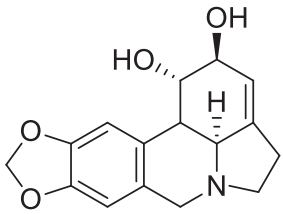
and MHV-A59 was reported. Emetine and lycorine exhibited their antiviral potential by inhibiting the synthesis of RNA, DNA, and protein of virus and by stopping the cell division, respectively. However, mycophenolate mofetil showed its action by suppressing the immune effect on different CoV species [33] (Fig. 4.6).

Lycorine and pretazettine were extracted from *Clivia miniata* and *Narcissus tazetta*, respectively, and reported for their anti-HSV potential via cytotoxic protein synthesis [34–36] (Fig. 4.7).

Three potent anti-HSV alkaloids, i.e., oliverine, pachystaudine, and Oxostephanine (Fig. 4.8), were isolated from *Polyalthia oliveri*, *Pachypodanthium staudi*, and *Stephania japonica*, respectively. They showed their antiviral potential by inhibiting or delayed the synthesis of protein assembly of virions [37].



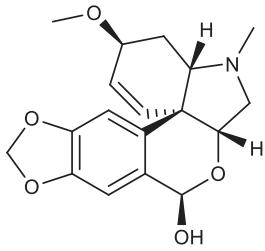
Emetine



Lycorine

Fig. 4.6 Structures of emetine and lycorine

Fig. 4.7 Structure of pretazettine



Pretazettine

Flavonoids

Flavonoids are basically the chromone-based polyphenolic phytochemicals, consisting 15-carbon skeleton with C6-C3-C6 pattern (Fig. 4.9). However, in some flavonoids, five-membered ring replaces the six-membered heterocyclic ring C. The C2 is directly bonded to the oxygen atom to form a furan moiety called aurone.

Flavonoids are classified on the basis of substitution pattern on ring C and their mode of oxidation. The flavonoids class of phytochemicals is considered as the largest group of antiviral agents in the whole plant kingdom. Flavonoids exhibits their biochemical potential by inhibiting various enzymes like xanthine oxidase, aldose reductase, lipoxygenase, cyclooxygenase, phosphodiesterase, Ca^{+2} -ATPase, etc.

The antiviral potential of flavonols are more as compared to the flavones against HSV, and their activity order is quercetin < kaempferol < galangin [38]. Another study reported the anti-HSV-1 potential of 3,5,7-trihydroxyflavone, i.e., galangin, extracted from *Helichrysum aureonitens*. This flavone also exhibited antiviral potential against Cox B1 at 12–47/μg/ml [39]. A study showed that the natural flavonoids having molecular weight of about 2100 Daltons exhibited excellent antiviral activity against type 2 and type 1 herpes simplex virus (HSV) [40]. Structure-activity relationship for 28 flavonoids against HIV-1 and HIV-2 was developed. Results showed that the flavan-3-o1 was most potent in selective inhibition of HIV due to the role of OH group on the flavone moiety [41].

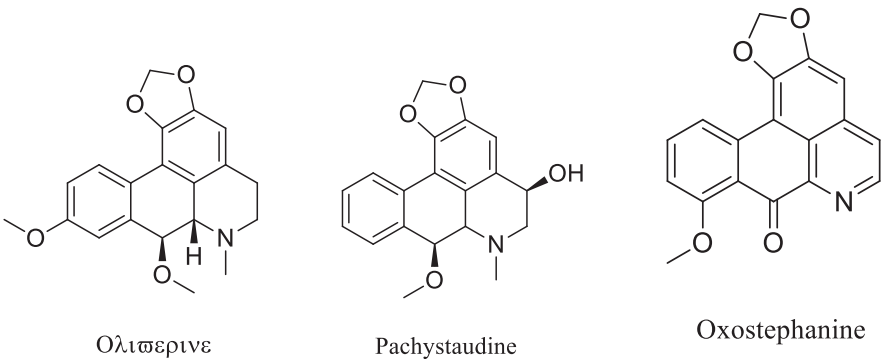
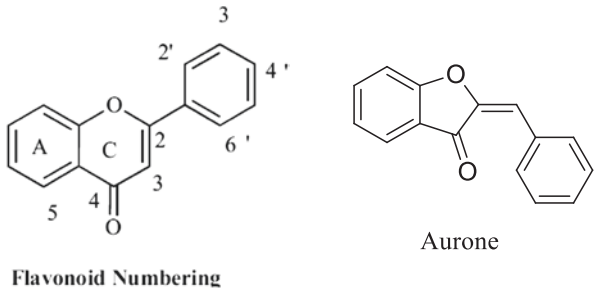


Fig. 4.8 Structures of oliverine, pachystaudine, and oxostephanine

Fig. 4.9 Structures of general flavonoid and aurone



Nineteen natural compounds were extracted from *Ranunculus sceleratus* and *Ranunculus sieboldii* and were investigated for their antiviral potential against hepatitis B virus (HBV) and herpes simplex virus (HSV-1). The experimental results revealed that apigenin 7-O-betaglucopyranosyl-4′-O-alpha-rhamnopyranoside, apigenin 4'-O-alpha-rhamnopyranoside, isoscopoletin, tricin, and tricin 7-O-beta-glucopyranoside showed significant antiviral potential against HBV replication (Fig. 4.10).

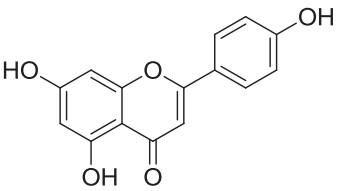
In addition, protocatechuic aldehyde exhibited antiviral activity by inhibiting the HSV-1 replication [39, 42, 43] (Fig. 4.11).

Classification of Flavonoids

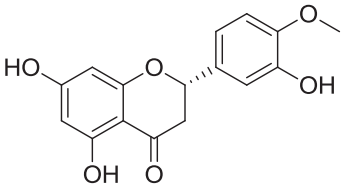
Chalcones

Chalcones as a major subclass of flavonoids are basically benzylideneacetophenone (1,3-diphenylpropenone) and its derivatives with basic formula ArCH=CHC(=O) Ar. Chalcones have been broadly investigated for their antiviral potential.

Chalcones also form basis for the biosynthesis of other flavonoids and isoflavonoids. Chalcones (Fig. 4.12) exhibited excellent antiviral potential [44]. They also

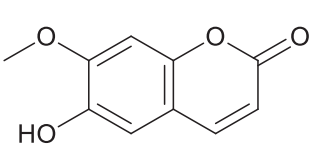


Apigenin

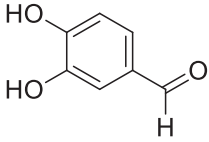


Hesperetin

Fig. 4.10 Structures of apigenin and hesperetin



Isoscopoletin



Protocatechuic aldehyde

Fig. 4.11 Structures of isoscopoletin and protocatechuic aldehyde

developed SAR for these chalcone pharmacophore models which were helpful to identify chemical signatures for the antiviral activity.

On the basis of these results, 44 chalcones exhibited inhibitory potency <100 μM, while 4 showed IC_{50} values <10 μM [45].

Different varieties of chalcones, i.e., kazinol (A, B, F, and J), broussochalcone (A and B), 3′-broussoflavan A, (3-methylbut-2-enyl)-3′,4,7-trihydroxyflavane, 4-hydroxyisolonchocarpin, and papyriflavonol A, were extracted from *Broussonetia papyrifera* and reported their antiviral activity against both SARS-CoV PL^{pro} and $3CL^{pro}$. The results reported the highest inhibition potential exhibited by papyriflavonol A against PL^{pro} with IC_{50} value 3.7 μM [46] (Fig. 4.13).

In another study, 4'-O-methylbavachalcone, psoralidin, bavachinin, corylifol, isobavachalcone, and neobavaisoflavone were extracted from *Psoralea corylifolia* and tested for their papain-like protease inhibitory action against SARS-CoV [47]. Among these isolated phytochemicals, psoralidin exhibited most potent inhibitory action against SARS-CoV, with IC_{50} value 4.2 μM (Fig. 4.14).

Dihydrochalcones

Dihydrochalcones were derived from its respective chalcone derivatives via a reduction of the C=C double bond (Figure). But as a result of reduction, its lost and chromophoric property as UV visibility is concerned as compared to its parent chalcone moiety. Dihydrochalcones extracted from *Millettia leucantha KURZ* (Leguminosae) exhibited potent anti-HSV activity [48] (Fig. 4.15).

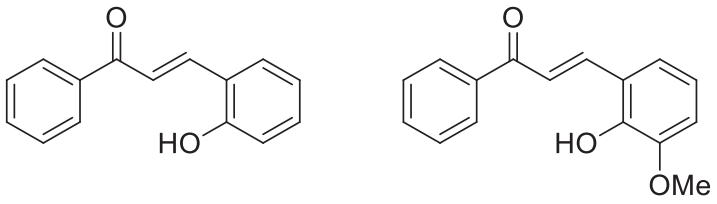


Fig. 4.12 Structure of different chalcones

Flavones

Flavones having 2-phenylchromen-4-one (2-phenyl-1-benzopyran-4-one) basic backbone constitute a significant class of flavonoid family. Flavones were mainly isolated from various plant families like Lamiaceae, Asteraceae, Apiaceae, etc. Many potent flavones were isolated from heartwood of *Artocarpus gomezianus* and studied for their anti-HSV activity. Among the identified compounds, artogomezianone (Fig. 4.16) exhibited the excellent antiherpetic properties [49].

Naringin (3′,4′-diacetoxy-5,6,7-trimethoxyflavone) having therapeutic properties especially for viral infections (e.g., HCV, HIV, respiratory virus, and *Picornavirus*). These flavones also used for the treatment of infections caused by parasites (e.g., toxoplasmosis) [50]. Methoxyflavones were studied for its SAR as anti-*Picornavirus* by means of molecular electrostatic potential (MEP) maps, and results showed that the antiviral properties are due to the negative MEP values especially in two regions, i.e., the first is in 3-methoxy (3-OMe) group, while the other is diagonally opposite to the substituent at C7 atom of the molecule [51] (Fig. 4.17).

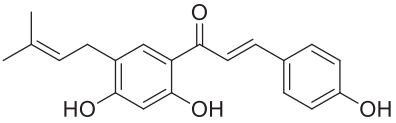
Antiviral potent flavones and biflavones extracted from *Torreya nucifera* showed their virucidal activity against SARS-CoV $3CL^{pro}$ [52]. Moreover, IC_{50} values of quercetin, luteolin, apigenin, and amentoflavone were 23.8, 20.2, 280.8, and 8.3 μM, respectively (Fig. 4.18).

Silybum marianum, a flavonolignan (also known as "silymarin" or "milk thistle"), was reported for its in vitro anti-HCV potential [53, 54] via exhibiting the significant effects on reducing the viral load [55–57].

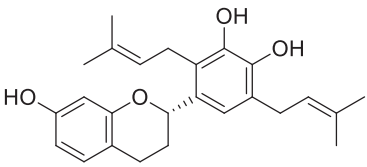
Three biflavonoids, i.e., stelleranol, genkwanol C, and genkwanol B, were extracted from *Radix Wikstroemiae* and reported their effective antiviral potential against RSV [58]. Various flavone 6-C-monoglycosides were isolated from *Lophatherum gracile* leaves and showed good viricidal activity against RSV infection, determined by cytopathic effect reduction assay [59].

Flavonones

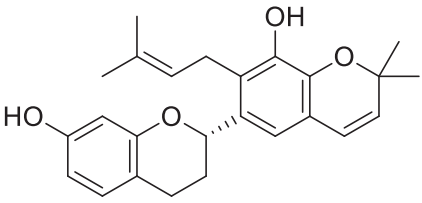
Flavonones consist of the same basic structural backbone as present in the flavones except the presence of the carbonyl moiety at the C4 carbon. Synthesis of flavanone derivatives of Abyssinone II (Fig. 4.19), a natural prenylated flavanone has been



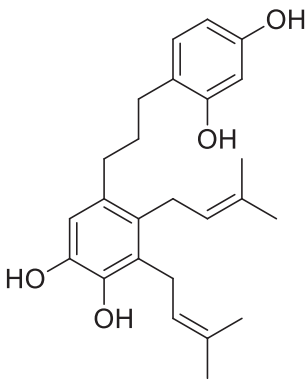
broussochalcone B



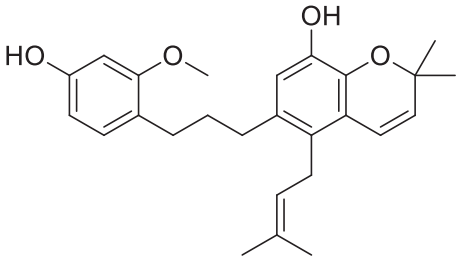
Kazinol A



Kazinol B



Kazinol F



Kazinol J

Fig. 4.13 Structures of broussochalcone B and kazinol (A, B, F, and J)

reported in literature. These analogs were tested against HSV-1 in HeLa 5 cells and reported their excellent antiviral potential [60].

A number of natural plants products, i.e., 6-geranyl-4′,-5,7-trihydroxy-3′,5′-dimethoxyflavanone, different types of tomentin (A, B, C, D, and E), mimulone, diplacone, 3’-O-methyldiplacone, 4’-O-methyldiplacone, 3’-O-methyldiplacol, and

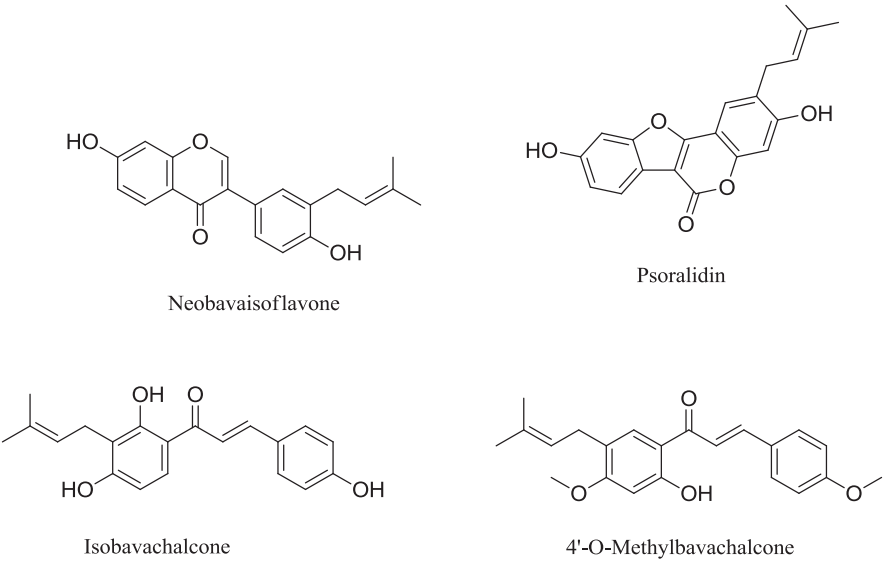


Fig. 4.14 Structures of neobavaisoflavone, psoralidin, isobavachalcone, and 4'-O-methylbavachalcone

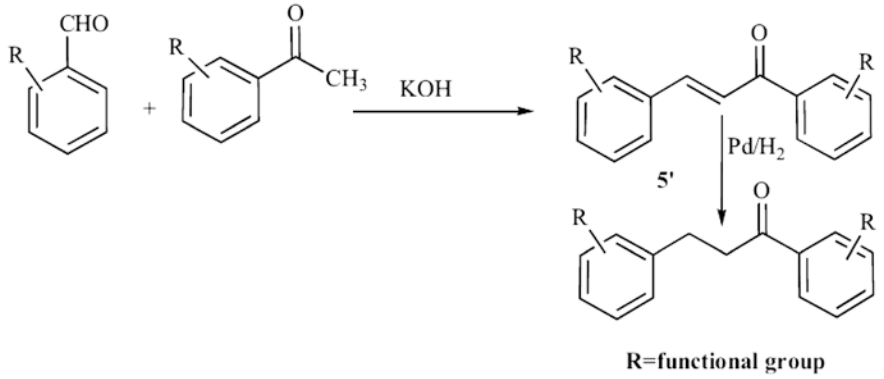


Fig. 4.15 Synthetic layout of dihydrochalcones

4'-O-methyldiplacol were extracted from *Paulownia tomentosa* and showed their antiviral therapeutic action by inhibiting the PL^{pro} of SARS-CoV [61] (Figs. 4.20 and 4.21).

In addition, juglanin also reported as an antiviral agent against SARS-CoV, by blocking the 3a channel of SARS-CoV having 2.3 μM IC_{50} value [62].

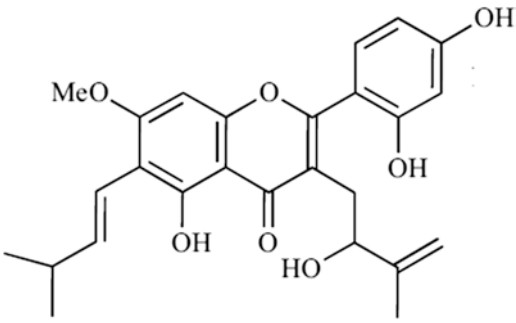


Fig. 4.16 Structure of artogomezianone

Artogomezianone

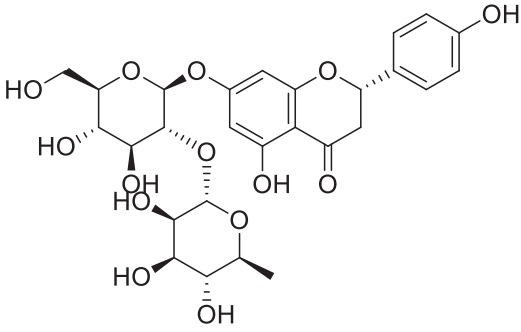


Fig. 4.17 Structure of naringin

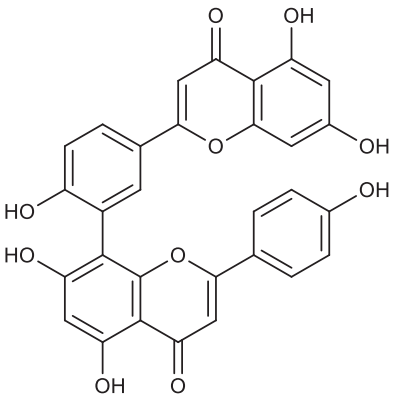
Naringin

Dihydroflavonols

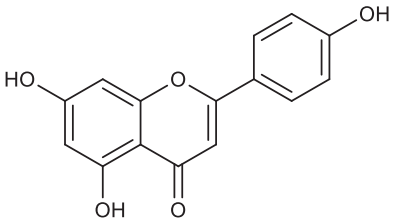
Dihydroflavonols (Fig. 4.22) are categorized by OH substituent at C3 of the flavonone pharmacophore. Flavanonols and their derivatives showed antiviral potential against various strains of viruses like hepatitis B, liver protection, mycotic infection, autoimmune disease, and inflammation disease [27].

Flavonol

Flavonol consists of identical basic structural backbone as present in the flavones having OH functional group at 3-position of the flavone. Quercetin (Fig. 4.23) exhibited the efficient antiviral potential against different viral strains like respiratory syncytial virus (RSV), poliovirus type 1, HSV-I, parainfluenza virus type 3 (Pf-3), etc. Quercetin not only reduced the intracellular replication but also triggered a concentration-dependent decrease in the viral infection [63]. Myricetin (3,5,7,3′,4′,5′-hexa-hydroxyflavone), a plant-derived flavonoid, has natural compound with potent nutraceuticals value and so is used in many foods and beverages.



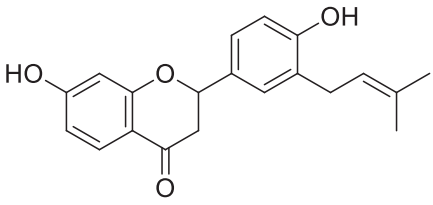
Amentoflavone



Apigenin

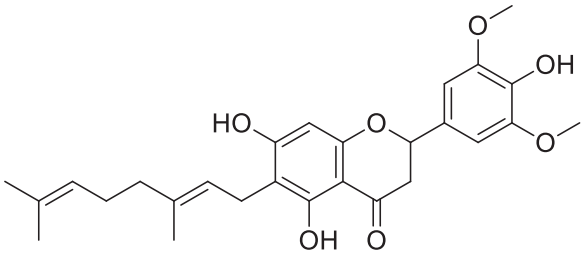
Fig. 4.18 Structures of amentoflavone and apigenin

Fig. 4.19 Structure of Abyssinone II



Abyssinone II

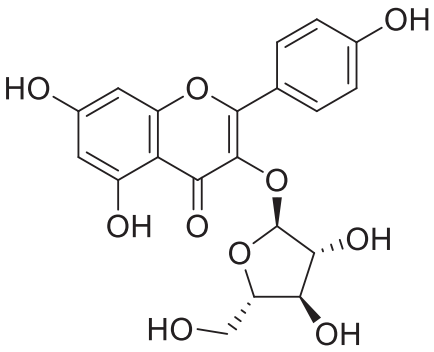
Fig. 4.20 Structure of 6-geranyl-4′,-5,7-trihydroxy-3′,5′-dimethoxyflavanone



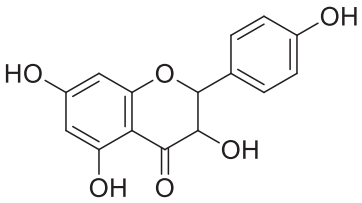
It is also used as preservative in oils and fats to increase the shelf life by acting as antioxidant. This phytochemical showed a wide range of bioactivities like antioxidant, anti-inflammatory, antidiabetic, and anticancer. This compound showed excellent therapeutic results against Parkinson and Alzheimer's disease. Myricetin also exhibited significant antiviral activity against coronavirus, influenza virus, and hepatitis B virus [64].

The natural phytochemicals cinnamtannin B1, procyanidin A2, and procyanidin B1 (Fig. 4.24) were extracted from *Cinnamomi cortex* and reported their antiviral potential against SARS-CoV [65].

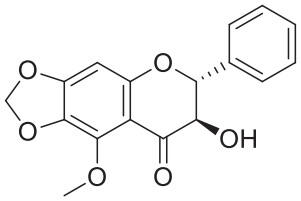
Fig. 4.21 Structure of juglanin



Juglanin



(+)-dihydrokaempferol



(2R,3R)-3-hydroxy-5-methoxy-6,7- methylenedioxyflavanone

Fig. 4.22 Structures of dihydroflavonol

Isoflavonoids

Isoflavonoids are the derivatives of flavonoids having phenyl group at 3-position instead of 2-position (Fig. 4.25) as a result of migration, with important therapeutic activities.

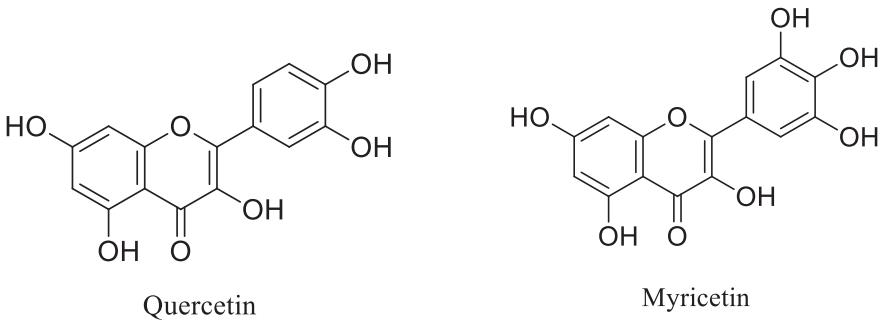


Fig. 4.23 Basic structures of quercetin and myricetin

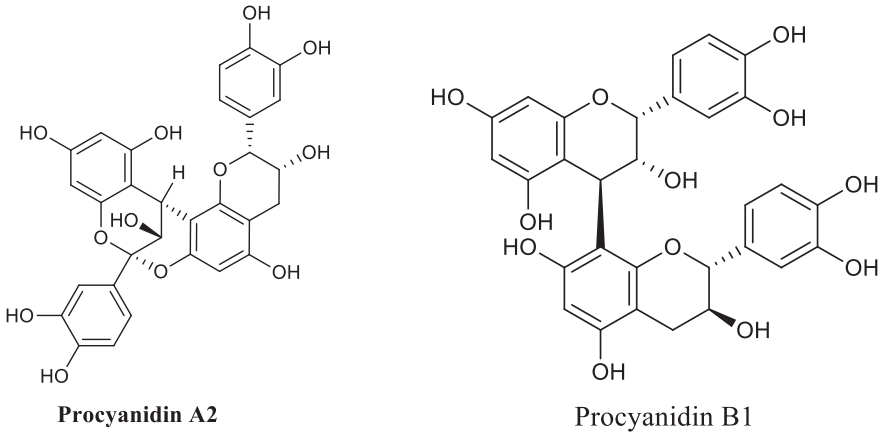


Fig. 4.24 Structure of procyanidin A2 and procyanidin B1

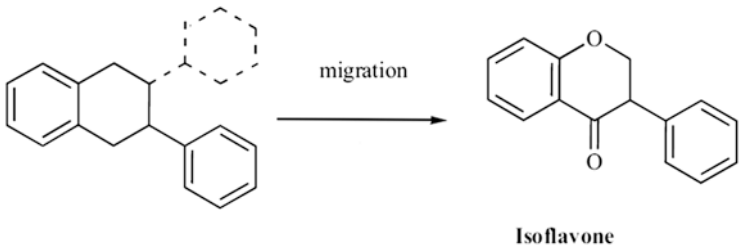
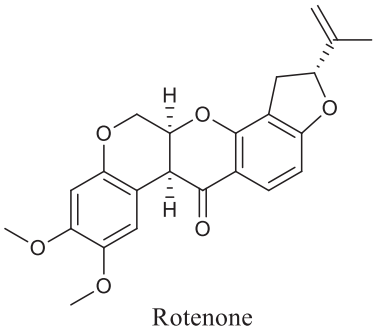


Fig. 4.25 Structure of isoflavones

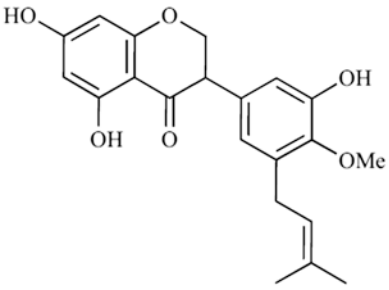
Isoflavones

Isoflavones (Fig. 4.25) are mainly isolated from the Leguminosae family. Rotenone (Fig. 4.26) showed excellent antiviral activity against Newcastle disease virus as tested by means of plate and tube assay methods [66].



Rotenone

Fig. 4.26 Structure of rotenone



Isoflavanone PMZ-1

Fig. 4.27 Structure of PMZ-1

Isoflavanones

Isoflavanones are consist of the same basic structural backbone as present in the isoflavones except the presence of the carbonyl moiety at the C4 carbon and also have chiral center at C3. A prenylated isoflavanone, i.e., PMZ-1, was extracted from *Bolusanthus speciosus* (Bolus Harms) and evaluated for its anti-HIV potential with wide therapeutic index (TI > 300) [67] (Fig. 4.27).

Neoflavonoids

Neoflavonoids are the class of flavonoids having aryl group at C_4. Four neoflavonoids, i.e., calophyllolide and inophyllums (Fig. 4.28), were isolated from *Calophyllum inophyllum* and tested for their antiviral potential against HIV-1 RT. The results showed that inophyllums (i.e., P and B) were the most effective with IC_{50} values of 0.130 mM and 0.038 mM, respectively [68].

AnthocyanidinAnthocyanidin (Fig. 4.29) consists of aglycone (anthocyanidine) backbone with glycone sugar moiety, an important class of plant pigments. Their biological potential is based on the coordination of free OH group with metal ions, e.g., Ca^{2+} and Mg^{2+}, in basic conditions.

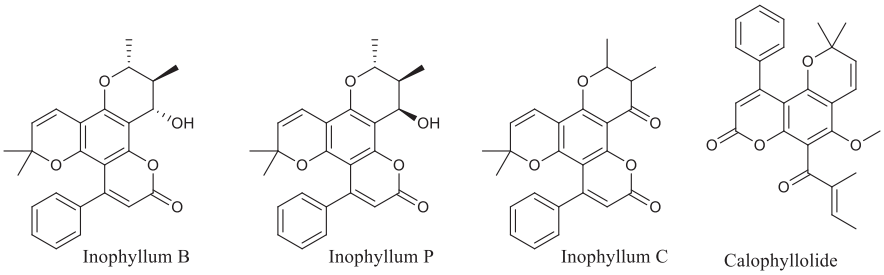


Fig. 4.28 Structures of (+) inophyllums B, (+) inophyllums P, (+) inophyllums C, and calophyllolide

Fig. 4.29 Structures of general anthocyanidin

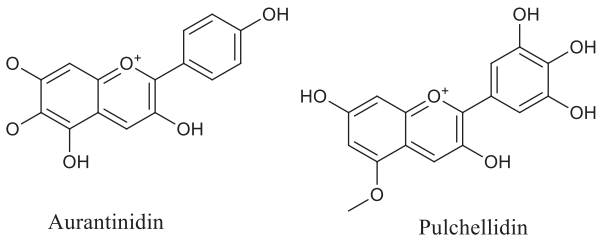
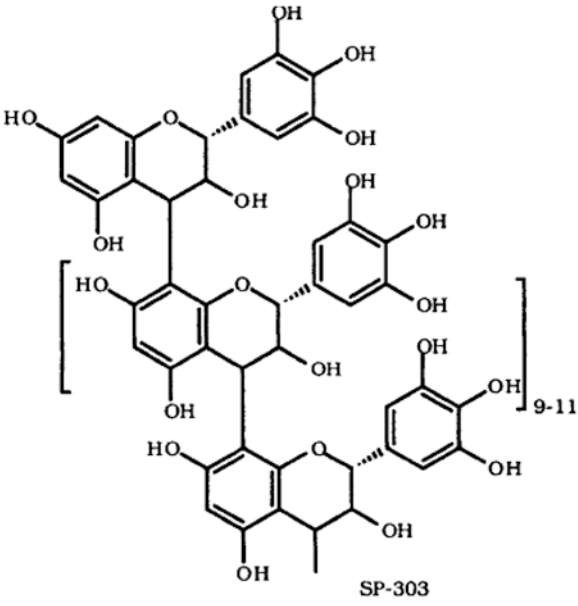


Fig. 4.30 Structure of SP-303



SP-303 (Fig. 4.30) is a mixture of oligomeric proanthocyanidins up to Mol. wt. 2100 Daltons. It is extracted from the latex of *Croton lechleri* and evaluated for its in vitro antiviral activity against various strains of RNA, DNA viruses, and HSV.

Virend, a topical formulation of SP-303, was evaluated in phase II clinical trials and used in combination with acyclovir for the treatment of genital herpes. But these trials were stopped later on due to no extra benefits of virend over using acyclovir alone [69].

Terpenoids

Terpenoids are abundantly natural-occurring secondary metabolites, having five-carbon isoprene units as basic skeleton, and classified according to the number of isoprene units present in a molecule.

These are basically classified into:

Monoterpenes (C10), 2 isoprene units with 10 carbon atom basic skeleton
Sesquiterpenes (CI5), 3 isoprene units with 15 carbon atom basic skeleton
Diterpenes (C20), 4 isoprene units with 20 carbon atom basic skeleton
Triterpenes (30), 6 isoprene units with 30 carbon atom basic skeleton
Tetraterpenes (40), 8 isoprene units with 40 carbon atom basic skeleton

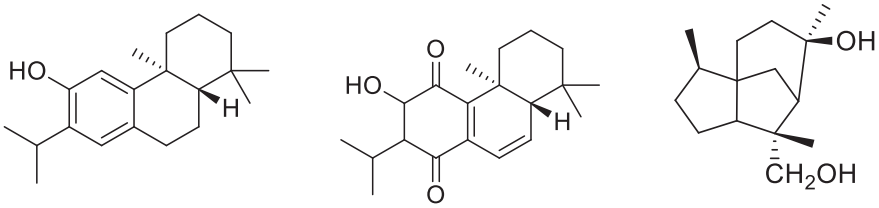
Sterols and saponins also classified as terpenoids.

Terpenoids possess diverse class of natural therapeutic phytochemicals. Many of the terpenoids were tested for their antiviral potential against severe acute respiratory syndrome (SARS-CoV) caused by coronavirus, and results showed their excellent antiviral potential (Fig. 4.31) [70].

These bioactive compounds also include abietane-type (diterpenes), labdane-type (i.e., both sesquiterpenes and triterpenes).

The saikosaponins (A, B_2, C, and D, 5–25 μM/L) exhibited potent antiviral activity against human CoV-229E, with EC_{50} values of 13.2, 19.9, 1.7, and 8.6 μM for D, C, B_2, and A, respectively. Saikosaponin B2 showed its antiviral activity by inhibiting the attachment and penetration stages of the virus [71] (Fig. 4.32).

According to the research report, carotenoids (tetraterpenoids, having 40-carbon polyene chain) like β-carotene, lycopene, α-carotene, and zeaxanthin/lutein (Fig. 4.33) increase the death rate during HIV infection [72].



Ferruginol 6-7-dehydroyleanone 3-beta cedran

Fig. 4.31 Structures of Ferruginol, 6-7-dehydroyleanone and 3-beta cedran

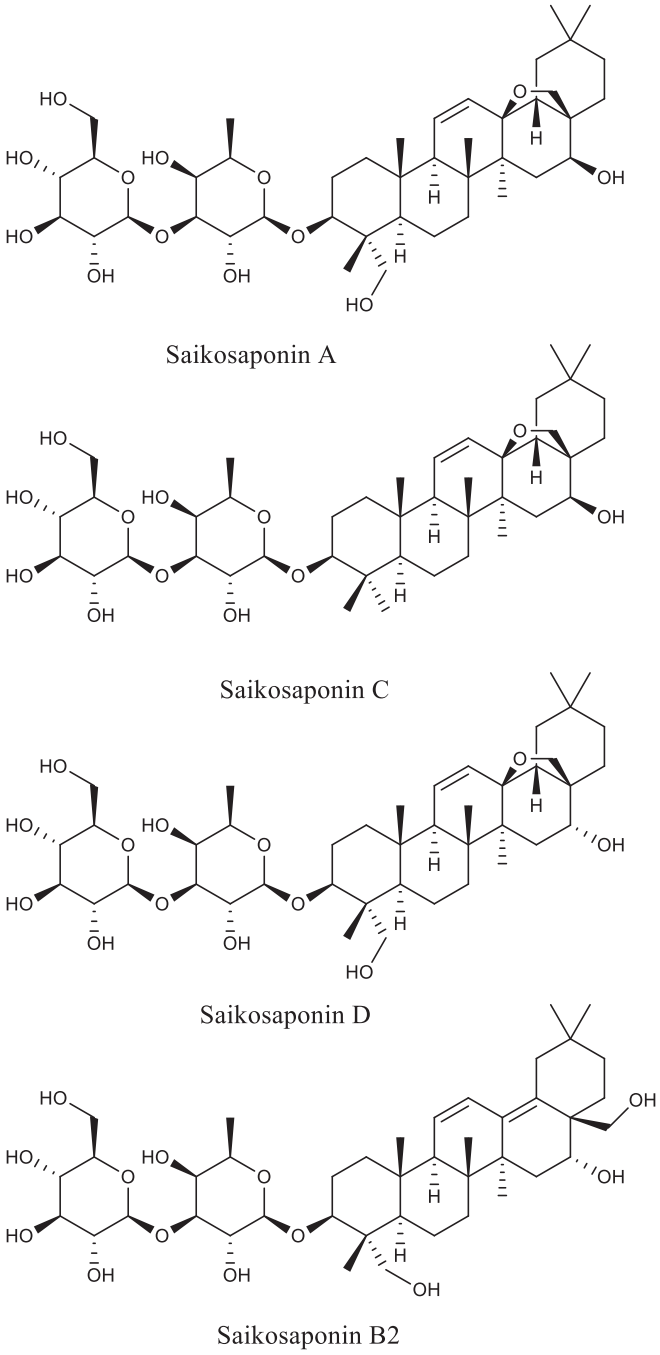


Fig. 4.32 Structures of saikosaponins (A, B_2, C, and D)

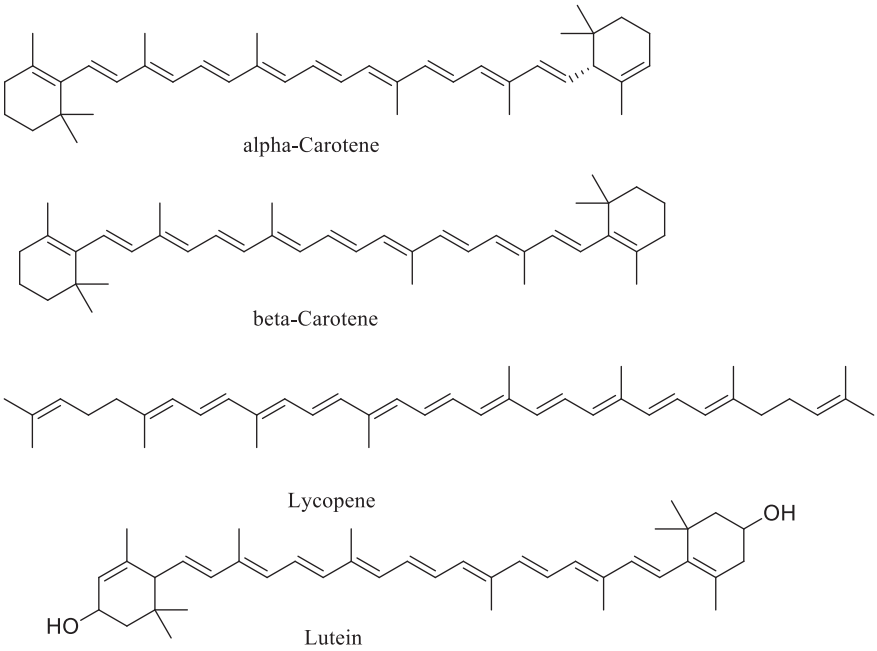
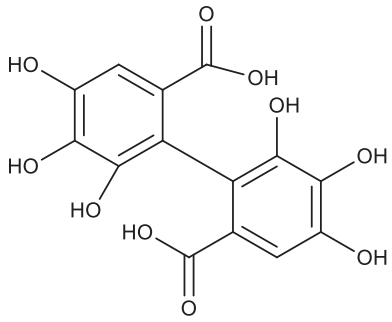


Fig. 4.33 Structures of α-carotene, β-carotene, lycopene, and lutein

Fig. 4.34 Structure of hexahydroxydiphenic acid



Hexahydroxydiphenic acid

Tannins

Tannins are basically high molecular weight phenolic compounds also containing other functional groups like (carboxyl, e.g., hexahydroxydiphenic acid), which give suitable property to coordinate for strong complex formation [73]. They are classified into two types, i.e., hydrolyzable and non-hydrolyzable (condensed). Hydrolyzable tannins, basically simple phenolic acids, are linked with the sugar moiety, for example, gallic acid. The condensed types have structural resemblance to flavonoids (Fig. 4.34).

Lemon balm (*Melissa officinalis*, Labiatae) is well known for its antiviral potential. This medicinal tannin containing plant is broadly studied. Leaves of lemon balm comprise 5 percent dry weight of tannins, in which caffeic acid is present as a main constituent. A cream having 1 percent dried leave extract of lemon balm has been introduced in Germany for the topical treatment of herpes infection of the skin [74].

Many tannin compounds like pentagalloylglucose, galloyl geraniin, sanguin, genothein B, punicalagin, punicallin, gemin D, etc. were reported for their antiviral potential against different chronic viral infections, i.e., HSV, HIV, and HIV-RT [75–80] (Fig. 4.35).

Seven ellagitannins were extracted from *P. urinaria* (Euphorbiaceae) and *Phyllanthus myrtifolius* and reported their antiviral potential against Epstein-Barr virus DNA polymerase (EBV-DP).

Dieckol, phlorofucofuroeckoln, eckol, and 7-phloroeckol isolated from *Ecklonia cava* displayed their antiviral activity by blocking the viral binding to porcine epidemic cells and reported experimental IC_{50} values of 14.6, 12.2, 18.6, and 22.5 μM, respectively [81] (Fig. 4.36).

Three polyphenolic compounds, i.e., tannic acid, 3-isotheaflavin-3-gallate, and theaflavin-3,3′-digallate (Fig. 4.37), were extracted from black tea and tested for their inhibitory action against SARS-CoV $3CL^{pro}$ with IC_{50} values of 9.5, 7, and 3 μM, respectively [82].

The hydrolyzable tannins, i.e., punicalagin and chebulagic acid which exhibited broad-spectrum antiviral potential, include RSV infection. These tannins showed their antiviral potential either by inactivating the RSV particles or by blocking the viral entry into the host cell, i.e., binding and fusion. Interestingly, both punicalagin and chebulagic acid were reported as futile against RSV postinfection spread. However, they are still effective against measles virus (MV, paramyxovirus) postinfection spread [83] (Fig. 4.38).

Punicalagin and chebulagic acid also exhibited anti-HSV-1 potential and showed their virucidal activity by acting as a glycosaminoglycan (GAG) competitors, so inhibiting the entry as well as cell-to-cell spread. Both directly targeted the HSV-1 glycoproteins which interact with glycosaminoglycan and inhibit the binding receptors [10].

Vitamins

Vitamin E includes eight isomeric derivatives, i.e., tocopherols and tocotrienols. They are fat-soluble and act as an excellent antioxidant. Vitamin E improves the immune system of the human body (Fig. 4.39). Vitamin E supplementation could be used as therapeutic agent for chronic hepatitis B [84].

Vitamin C also acts an antioxidant and enhances the immune defense against many infectious diseases [85] (Fig. 4.40).

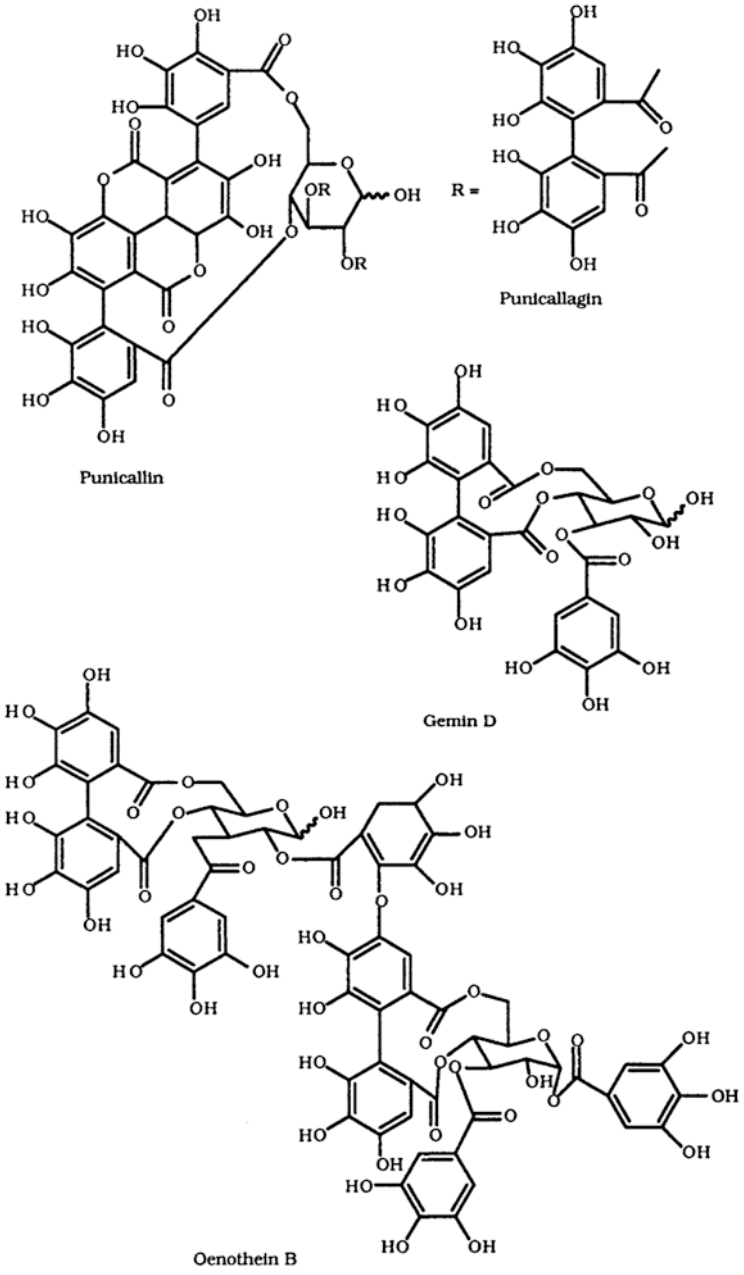


Fig. 4.35 Structures of punicalagin, gemin D, and genothein B

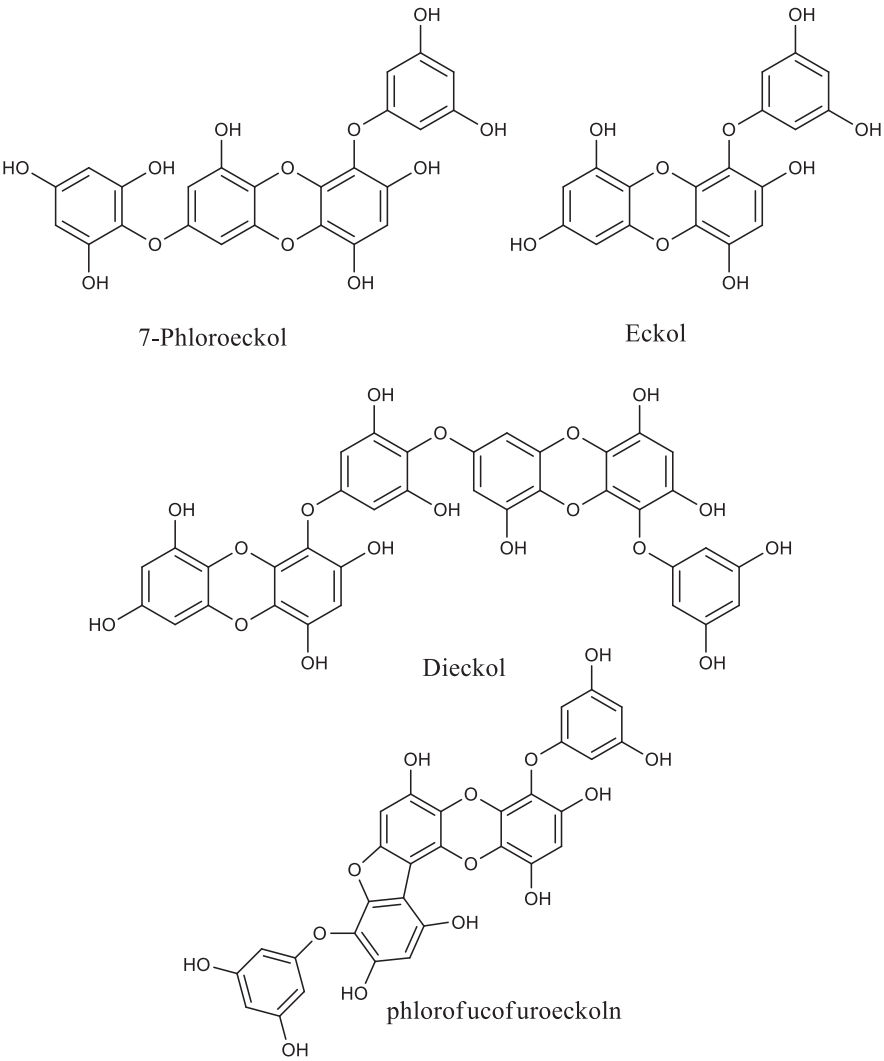
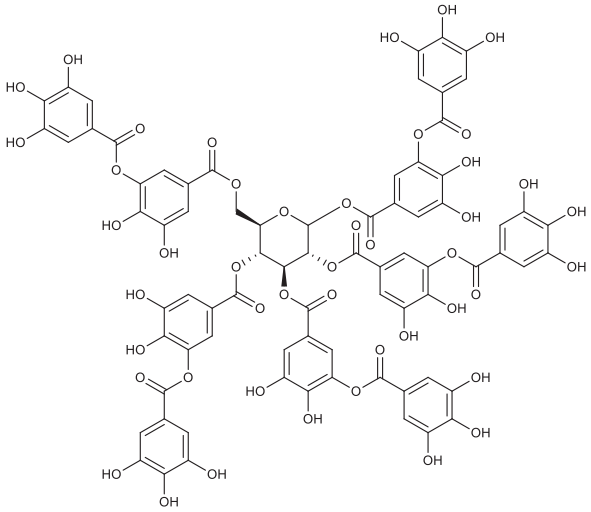


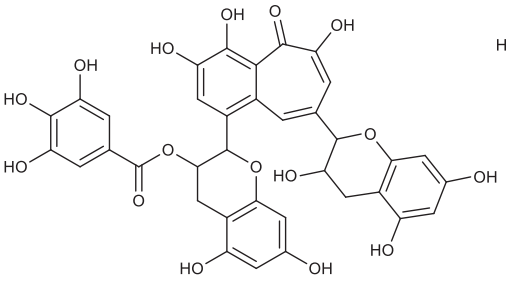
Fig. 4.36 Structures of 7-phloroeckol, eckol, dieckol, and phlorofucofuroeckoln

Vitamin C not only boosts the immune systems but also exerts anticancer, antibacterial, and antiviral activity [86–90]. In a comparative research study, antiviral potential of vitamin C against influenza virus type A, HSV-1, and poliovirus was reported. The decreasing sensitivity order of vitamin C was as follows: influenza virus> HSV-1 > poliovirus [91].

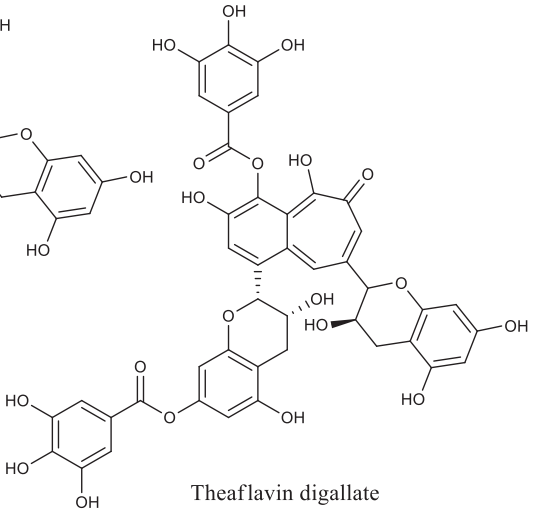
Dehydroascorbic acid (DHA) is an oxidized form of ascorbic acid. It is reported that DHA showed more potent antiviral activity against HSV-1 and influenza virus as compared to vitamin C (ascorbic acid), due to its stronger chemical stability of



Tannic acid



Isotheaflavin 3'-gallate



Theaflavin digallate

Fig. 4.37 Structures of tannic acid, 3-isotheaflavin-3-gallate, and theaflavin-3,3′-digallate

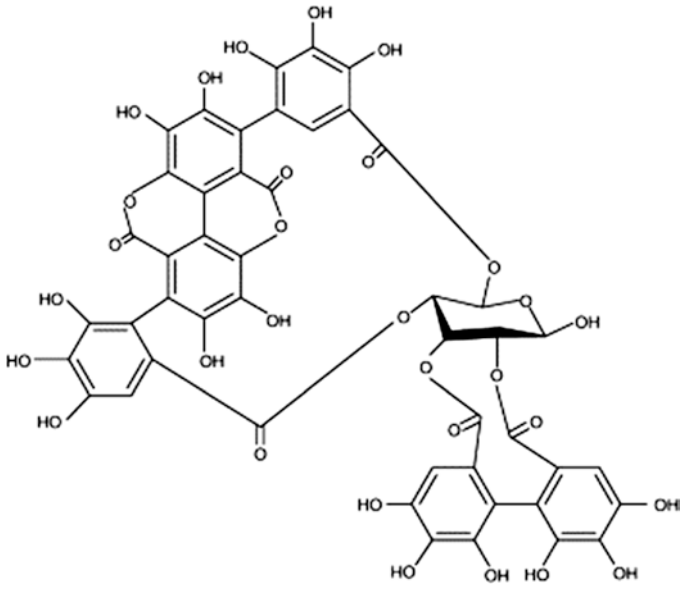


Fig. 4.38 Structure of punicalagin

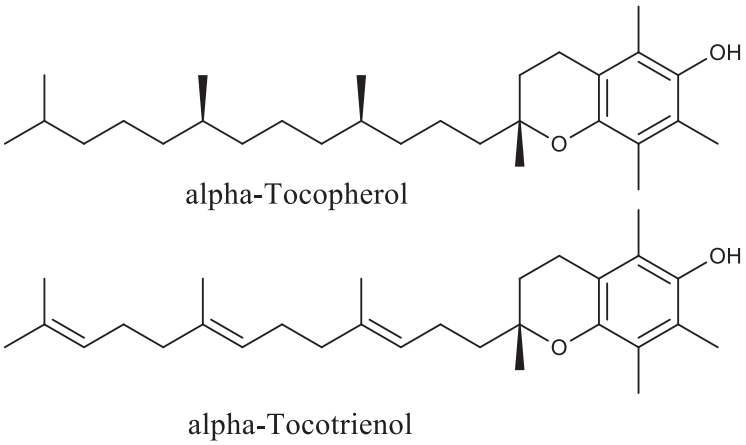
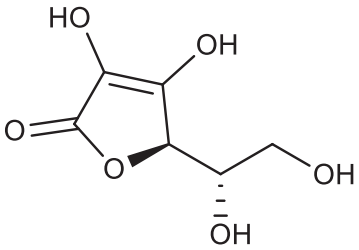


Fig. 4.39 Structure of vitamin E (i.e., tocopherol and tocotrienol)



Vitamin C

Fig. 4.40 Structure of vitamin C

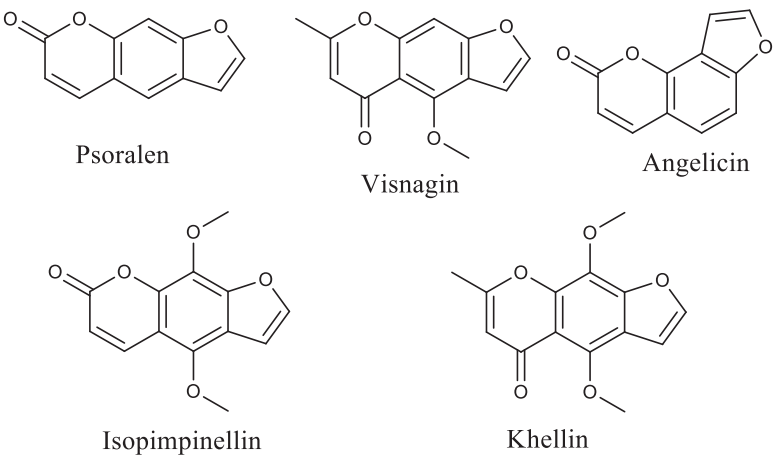


Fig. 4.41 Structures of psoralen, isopimpinellin, khellin, visnagin, and angelicin

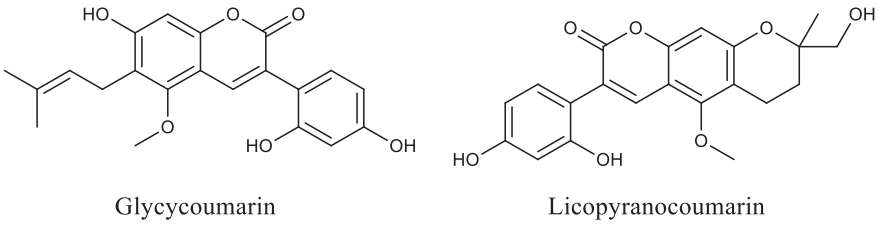


Fig. 4.42 Structures of glycycoumarin and licopyranocoumarin

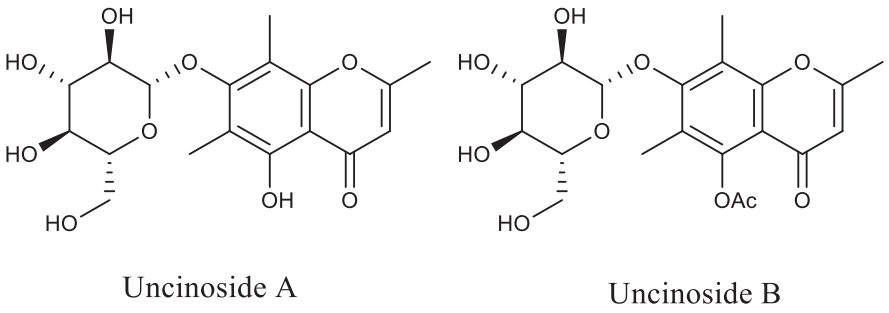


Fig. 4.43 Structures of uncinosides A and B

Table 4.2 Organosulfur phytochemicals isolated from Brassicaceae family and *Allium* [96]

Sr. no	Compounds	Type of compounds	Natural source
1.	Glucobrassicin	Glucosinolates	Cauliflower, Brussels, mustard, cabbage, choy, kale, water garden cress, sprouts, Bok, radish
2.	Allyl sulfides Dithiolethiones	Sulfides	Garlic, broccoli, onion
3.	Sulphoraphanes Phenylethyl Isothiocyanates	Isothiocyanates	Cabbage, kale, cauliflower, radish, Brussels, mustard, water garden cress, bok choy, sprouts

DHA. So results suggested that the antiviral potential of vitamin C is not only of its antioxidant property.

Chromones and Coumarins

Chromones and furanocoumarins are commonly present phytochemicals in various plant families. These natural compounds are abundantly found in families Umbelliferae and Rutaceae. According to research study, Khellin and visnagin were isolated from *Ammi* species (Umbelliferae) and reported their antiviral activities [92]. Psoralen, isopimpinellin, 8-methoxypsoralen, coriandrin, and angelicin were extracted from *Coriandrum sativum* and tested their antiviral potential against HIV, DNA, and RNA viruses and bacteriophages [93] (Figs. 4.41, 4.42, and 4.43).

Two potent anti-HIV coumarins, i.e., glycycoumarin and licopyranocoumarin, were isolated from *Glycyrrhiza Glabra* [94].

According to research study, two chromone glycosides, i.e., uncinosides A and B, were extracted from *Selaginella uncinata* and reported their potent antiviral activity against respiratory syncytial virus (RSV) infection [95].

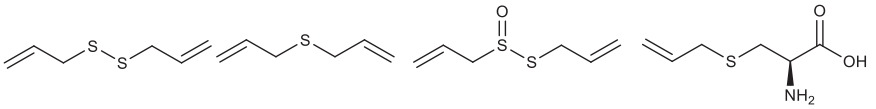


Fig. 4.44 Structures of diallyl disulfide, diallyl sulfide, allicin, and s-allylcysteine

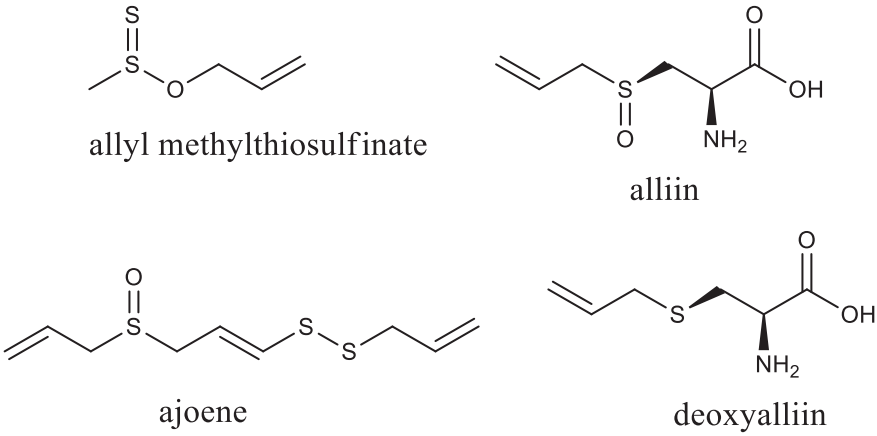


Fig. 4.45 Structures of allyl methyl thiosulfinate, ajoene, deoxyalliin, and alliin

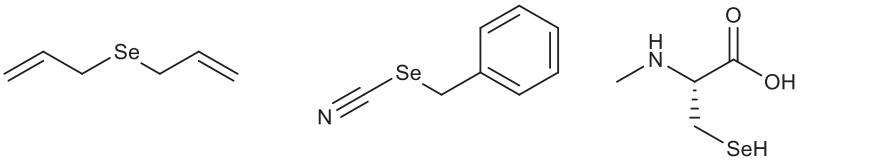
Organosulfur Compounds

Phytochemicals having sulfur atom are mainly isolated from Brassicaceae family and *Allium* (Table 4.2). The organosulfur phytochemicals having pungent odor are chemically unstable. The organosulfur compounds possess excellent antiviral potential [96]. A handsome number of organosulfur compounds showed antiviral activities (Fig. 4.44).

Various unsymmetrical alkyl-aryl disulfides were synthesized and then oxidized into thiolsulfinate [97].

A considerable large number of organosulfur compounds were isolated from fresh garlic extract like diallyl thiosulfinate, diallyl disulfide, diallyl trisulfide, allyl methyl thiosulfinate, alliin, allicin, deoxyalliin, and ajoene. These compounds were then evaluated for their in vitro virucidal potential [98] (Fig. 4.45).

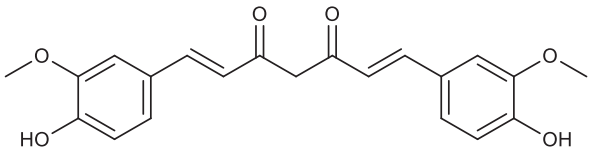
The antiviral mechanistic action of garlic containing phytochemicals against selected strains of viruses, i.e., HSV type 1 and type 2, vesicular stomatitis virus, human rhinovirus type 2, vaccinia virus, and parainfluenza virus type 3, were reported. The results indicated that in vitro virucidal activity depends upon the type of viral envelope and the cytotoxicity may depend upon the cell membrane. Virucidal activity is shown by inhibition of viral penetration or adsorption for non-enveloped



Diallylselenide Benzylselenocyanate Methylselenocysteine

Fig. 4.46 Structures of diallylselenide, benzylselenocyanate, and methylselenocysteine

Fig. 4.47 Structure of curcumin



Curcumin

virus. The increasing virucidal activity order was ajoene > allicin > allyl-methyl thiosulfinate.

Selenium Compounds

Selenium compounds also have antiviral potential against different strains of viruses. Various different selenium compounds with effective antiviral activity are shown in Fig. 4.46.

The experimental results of these compounds against different viral infections demonstrate the significance of selenium-based compounds. Antiviral potential of three selenium compounds against *Coxsackievirus* was B5 reported via targeting their replication rate [99, 100]. Selenite inhibited the replication of *Coxsackievirus* B5 more effectively, while selenomethionine and selenite did not show any significant antiviral potential. Ebselen derivatives were synthesized and tested for their in vitro antiviral potential. The results demonstrated that few tested analogs efficiently target the herpes simplex virus type 1 (HSV-1) and encephalomyocarditis virus (EMCV) by inhibiting the cytopathic activity [101].

Miscellaneous Antiviral Phytochemicals

Curcumin and Its Derivative

Curcumin is one of the important constituents of turmeric. Different analogs of curcumin showed significant antiviral activity against HIV-1 integrase [102]. Curcumin also shows anti-HCV potential by inhibiting the replication of HCV,

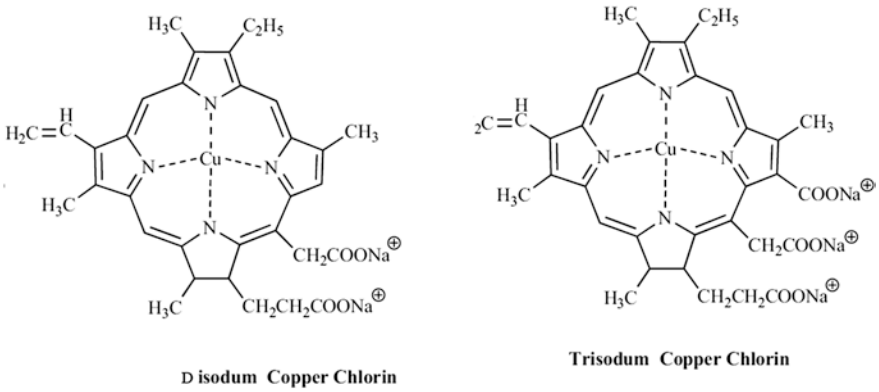


Fig. 4.48 Structures of disodium copper chlorin and trisodium copper chlorin

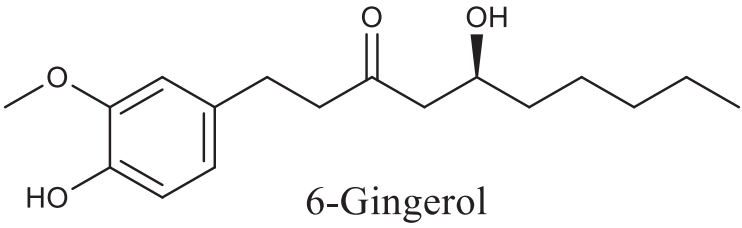


Fig. 4.49 Structure of 6-gingerol

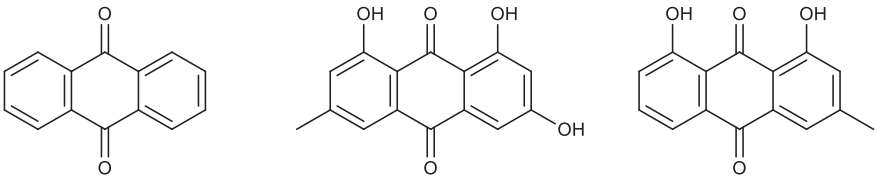
targeting the suppression of sterol regulatory element binding protein-1 (SREBP-1) Akt pathway [103] (Fig. 4.47).

Chlorophyllin

Synthetic derivative of chlorophyll, i.e., chlorophyllin (CHLN) (Fig. 4.48), has antimutagenic activity against various environmental pollutants. Chlorophyllin was evaluated for virucidal activity against poliovirus by inhibiting the nuclear fragmentation (NF) in HEp-2-infected cells [104].

Gingerols

Gingerols (Fig. 4.49) have been isolated from ginger and traditionally have been used for the treatment of throat infections and common colds. Gingerols also form an important ingredient of Ayurvedic formulations. Gingerols reported excellent antiviral activity against many strains of viruses [105].



Anthraquinone Emodin Chrysophanic

Fig. 4.50 Structures of anthraquinone, emodin, and chrysophanic

Chitin and Chitosan

Chitin, a natural polysaccharide, has partially deacetylated amino sugar *N*-acetylglucosamine basic skeleton, while chitosan is the deacetylated form of chitin. A research study on SCM chitin III (i.e., carboxymethyl chitin having 7.66% degree of sulfation) as its antiviral potential against HSV and Friend murine leukemia helper virus (F-MuLV) was reported [106].

Anthraquinone

Anthraquinone (9, 10-dioxoanthracene Fig. 4.50) is an anthracene derivative. Chrysophanic acid (1,8-dihydroxy-3-methylanthraquinone) is extracted from *Dianella longifolia* and tested for its in vitro antiviral activity against poliovirus types 2 and 3 by inhibiting the viral replication. Emodin was extracted from genus *Polygonum* and *Rheum* and exhibited excellent potential for the treatment of severe acute respiratory syndrome (SARS), which is caused by novel coronavirus (SARS-CoV). A type I membrane-bound protein, i.e., SARS-CoV spike (S) protein, is necessary for the attachment of virus to the angiotensin-converting enzyme 2 (ACE2) receptor of the host cell. Emodin effectively blocked the interaction of S protein with ACE2. It also showed significant inhibitory antiviral action against S protein-pseudotyped retrovirus to Vero E6 cells [107, 108].

Conclusion

In this chapter, we have discussed antiviral agents belonging to the different classes of natural phytochemicals like alkaloids, terpenes, flavonoids, tannins, vitamins, etc. There lies a huge scope in the development of new antiviral drugs due to the dire need. Nature has preserved a huge range of therapeutic natural compounds in the plant body. The coronavirus pandemic has enforced the scientific community to search for new antiviral agents. The work described herein is the sum-up of literature data described in previous few decades for the antiviral natural products and is expected to be useful for researchers working to develop new antiviral products.

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