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REVIEW

Phytochemicals from Medicinal Plants as Antiviral Agents: Recent Trends and Advancements

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Many compounds from therapeutic plants have been studied as potential antiviral agents. To control the spread, phytochemicals are employed to decrease viral copy production. This evaluation will be helpful to the scientific community's investigations into microbes and their infection. Other common viruses that are impacted by the phytochemicals of medicinal plants include herpes simplex, DNA viruses, poliovirus, cytomegalovirus, influenza, para-influenza type 3 and herpes simplex. The root of the plant is the most important and effective part for manufacturing strong phytochemicals. This review provides an overview of a number of phytochemicals, their synthesis and their medicinal qualities, which offer a wide range of therapeutic effects for the treatment of various viral infections. The phytochemical and pharmacological properties of these drugs are the subject of research aimed at identifying the essential chemical constituents and substantiating the efficacy and safety of these claims. Thus, there is promise for the future of medicinal plants because they have the potential to outperform chemical-based allopathic treatments.

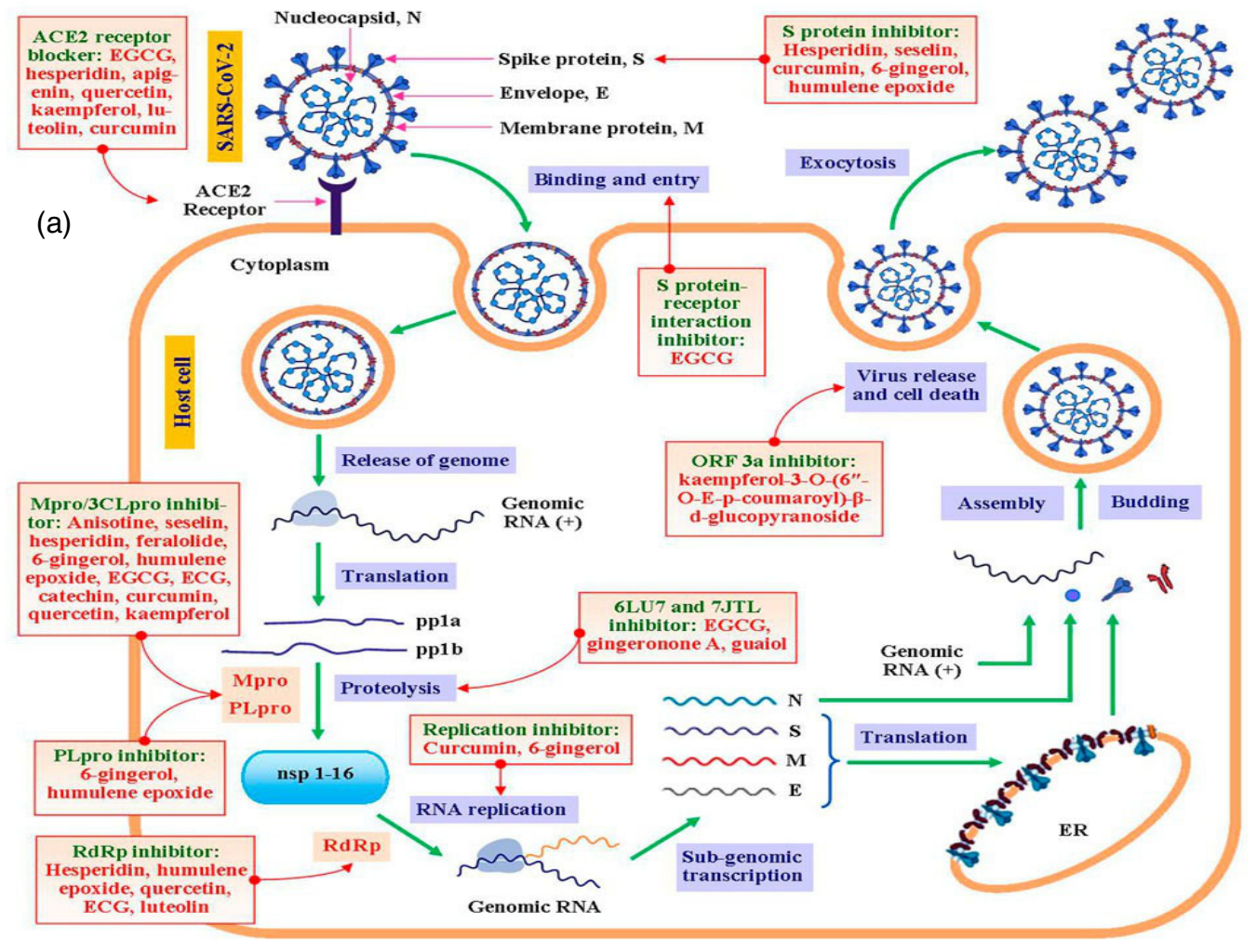
Keywords: Antivirals, Novel agents, Herbs, Natural plants, Antiviral activities, Viruses, Antimicrobial effects.

INTRODUCTION

Nowadays, viral infection has become a major global issue to healthcare system due to uncontrolled mortality rate [1]. Human health has been impacted in the past by a number of dangerous viruses, including herpes simplex virus (HSV), human immunodeficiency virus (HIV) and hepatitis A, B and C viruses (HAV, HBV and HCV) [2,3]. Novel coronavirus (SARS-CoV-2) is one of these viruses which have started to become a global issue from 2019 [4,5]. Gisondi *et al.* [6] demonstrated that the novel coronavirus disease (COVID-19) is characterized by severe acute respiratory syndrome that results in a very high death rate. For instance, each year influenza virus causes around 3 million new cases of serious illness and amid 300,000 and 500,000 fatalities [7-9]. Alarmingly, the usage of hypodermic syringes, blood transfusions and organ transplants are all contributing to an increase in the number of people with viral infections every year [10,11]. Many other viruses don't currently have any effective treatments and the only vaccines available are for the hepatitis A, varicella and mumps [7]. These medications also frequently come with adverse effects are expensive and are ineffectual owing to virus resistance. Therefore, there is increasing interest in testing for phytochemicals as natural antiviral compounds [12,13]. Recently,

the problem of viral diseases has been controlled by the use of medicinal plants and their bioactive metabolites [14,15]. Indigenous traditional herbal medicine has a long history of treating a wide range of chronic and infectious disorders including urinary tract infection [16,17]. As a result, the search for new antiviral medicines concentrates on both synthetic combinations and metabolites originating from the medicinal plants. Hussain *et al.* [18] studied effective plant metabolites which have the ability to prevent the replication of viruses with negligible negative effects on the physiology of host. Scientists have reported several medicinal plants with antiviral activities like *Xanthoceras sorbifoli*, *Dioscorea bulbifera*, *Wistaria floribunda* and *Aegle marmelos* showed a significant antiviral activity [19]. Phytochemicals such as alkaloids, tannins, terpenes, steroids, polyphenols, quinones, saponins, polysaccharides, coumarins and thiosulfonates were reported in medicinal plants which showed antiviral activities [20]. Currently, Das *et al.* [21] also demonstrated the inhibition of SARS-CoV2 viral infection with natural antiviral medicinal plants metabolites.

Antiviral mechanisms of phytochemicals: The virus enters the host cells by adhering to the receptors first, then penetrating through the cell wall to enter the interior, where the virus uncoils [22,23]. The virus' genetic material fuses with the genetic material of the host cell and interfere with the replication, transcription and translation processes that control gene expression [24-26]. Numerous well-known plant bioactive isolates, including flavonoids, terpenes, lignins, steroids, polysaccharides, tannins, saponins and polyphenols, have been found to combat viral infections [27]. By regulating virus adsorption, preventing virus attachment to plant cell receptors, or interfering with the pathways involving the activation of intracellular signals, these therapeutic metabolites have the ability to prevent viral replication [28,29]. The glycans on the HIV and HCV envelopes are hidden by carbohydrates-binding agents, which results in deletions in the glycan envelope and further stimulates the immune system of the host cells to attack the epitopes on the viral envelope [30]. Different tactics have been used to manage viral infection. Viral binding sites or host receptors can be blocked to prevent viral attachment [31]. At various stages of infection, a virus can be blocked. Some of the tactics specifically target DNA/RNA polymerase, viral protein posttranslational modification, or viral assembly in an effort to prevent viral reproduction [32]. Phytochemicals have used a number of ways to prevent viral replication. For example, RNA polymerase, protease and reverse transcriptase are just a few of the viral and host enzymes that epigallocatechin gallate (EGCG) inactivates (Fig. 1). Another method used by flavonoids is to prevent protein phosphorylation, which limits HIV replication.



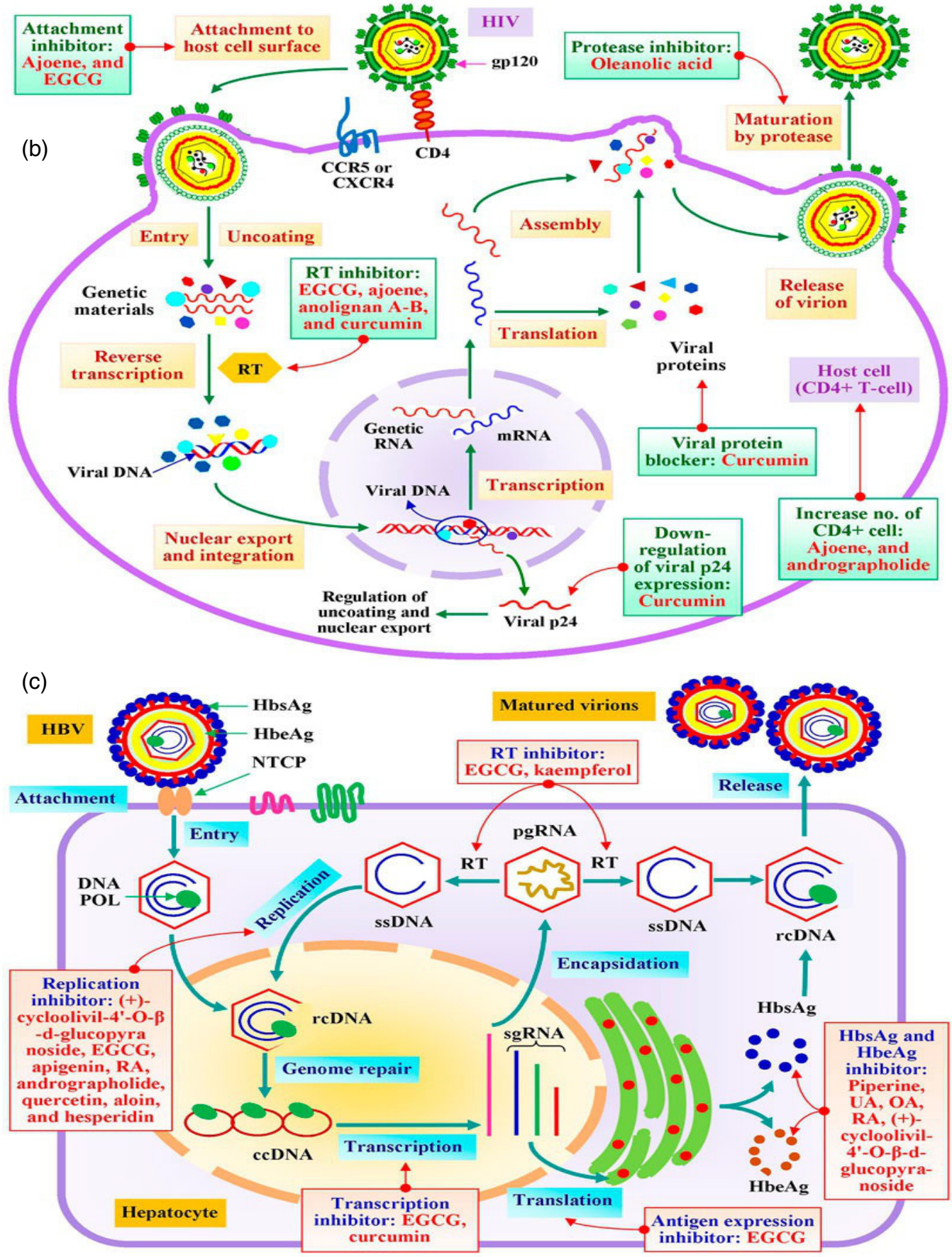


Fig. 1. Mechanistic insights of phytochemicals working as anti-viral agents [40]

For instance, Herpes Simplex Virus 1 gene expression is inhibited by samarangenin B, which is isolated from the roots of *Limonium sinense* (Sea lavender) [33-35]. Glycyrrhizic acid present in the roots of *Glycyrrhiza radix* inhibited the replication of Epstein-Barr virus [36]. Pterocarnin A, a compound isolated from the bark of *Pterocarya stenoptera* prevents the attachment and penetration of Herpes Simplex Virus 2 into the host cells [37]. *Tanacetum vulgare* rhizome extracts include spiroketal-enol ether compounds, which prevent virus entrance and stop the production of HSV-1 glycoprotein C and HSV-2 glycoprotein G [38]. Terpenoid from the roots of *Bupleurum kaoi*, such as Saikosaponin B2, neutralizes the viral particles and prevents virus attachment and subsequent entry into the host cell [39]. The toxicity of these phytochemicals in humans and animals must be studied in order to assess their efficacy in whole-organism systems.

Synthesis of major phytochemicals: Phytochemicals are obtained from plants during the process of metabolism which produces large number of intermediate metabolites such as primary and secondary metabolites [41,42]. These metabolites signify the chemical pathways occuring in plants (Figs. 2 and 3). Most of the benzene containing compounds are biosynthesized by mainly three pathways (i) shikmic acid pathways; (ii) acetate mevalonate pathway, and (iii) acetate malonate pathway.

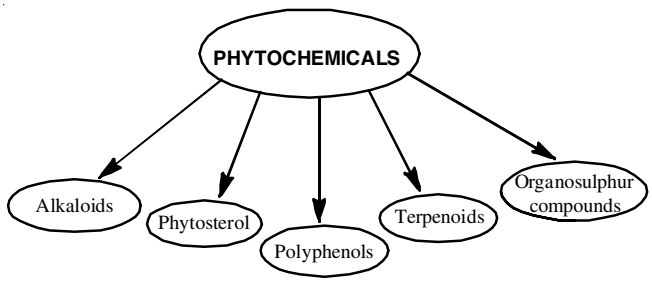


Fig. 2. Major classes of phytochemicals

The shikmic acid pathway occurs in the plasmid of higher plants which undergo photosynthesis by assimilation of CO_2 form glucose (sugars), which underwent glycolysis to produce precursors like erythrose-3-phosphate (EP) and phosphoenol pyruvate (PEP) [43]. Due to condensation reactions between EP and PEP phenylalaninie, tyrosine tryptophan are produces which form the nitrogen containing alkaloids, polyphenols (polyphenols are curcumin, ellagic acid, tannic acid), amino acids and pigments, *etc*. [44]. Acetate melvalonate pathway (also called as isoprenoid pathway) starts from acetyl coenzyme A produces two C-5 building blocks (acetyl CoA produces isopentenylpyrophosphate (IPP) and dimethylallylpyrophosphate (DMAPD) *via* squalene), which are used to produce 2 different types of compounds such as steroids and terpenoids and other products [45,46].

Third pathway acetyl-malonate pathways start from acetyl CoA which is modified to give malonyl CoA act as precursor for fatty acids synthesis to produce linear polyketide chin and no of fatty acids. Acetyl Co A through th citric acid cycle also produces 20 nitrogen and -COOH containing amino acids as well as organosulphur compounds like glucosinolates, allylic sulfides, *etc*. [47,48]. Plants can synthesize all 20 amino acids but mammals can only synthesize 10 amino acids, which further act as precursors for alkaloids.

Methodology to search antiviral phytochemicals: The primary chemical classes of phytochemicals that act as antiviral drugs are discussed in this section. In particular, the effects of several phytochemicals on viral illnesses that are still prevalent today were examined, with many instances displaying hopeful results in this field. Searching through articles in PubMed, Google Scholar and Scopus provided the information. The electronic databases were searched and 600 articles were found. We include antiviral peptides, thiophenes, polyenes, alkaloids, saponins, coumarins, polyphenolics, flavonoids, sulphides, lignans, terpenoids, *etc*. as they have antiviral effects. After applying the inclusion and exclusion criteria, a total of 74 studies were chosen for the investigation

Antiviral peptides: Despite the fast advancements made in human healthcare, the significant morbidity and fatality rates brought on by some viral infections highlight the need for novel antivirals to be developed [50,51]. Because of their poor response, rising rates of resistance and numerous unfavourable side effects, the available antiviral medications are restricted [52]. It is being investigated and seems hopeful that one of the recently developing fields, "peptide-based therapies" can combat viruses. Many scientific efforts have been made recently to use a variety of cutting-edge technologies to identify innovative and prospective peptide-based therapies [53,54]. Antiviral peptides (AVPs) are peptides that have the ability to avert the spread of viruses. AVPs often demonstrate antiviral actions by directly inhibiting the virus, although their inhibitory sites and mechanisms of action change depending on where in the viral replication cycle they act [55]. Numerous research projects are being carried out to clarify the function of peptides in preventing viral infections because the field of peptides as antivirals has not yet been fully investigated. The heptad-repeat (HR2) domain of gp41 (HIV envelope protein) corresponds to the 36-amino acid residue peptide enfuvirtide (Enf), the first peptide drug authorized for clinical use. HIV infection is inhibited by Enf, which stops the HR1 domain from fusing with HR2 during HIV formation [56]. In the same way, the FDA approved telaprevir and boceprevir in 2011 as synthetic peptides against the hepatitis C virus (HCV). These peptides prevent viral replication by interfering with a protease inhibitor (NS3/4) [57]. Other peptide drugs, including, Flufrvitide for the treatment of influenza [58], Thymosin-1 for the treatment of both HBV and HCV, myrcludex for the treatment of hepatitis B and D viruses (HBV and HDV) [59], IM862 and SCV-07 for the treatment of HCV and Sifuvirtide for the treatment of HIV-1 [60], are undergoing various stages of pre-clinical and clinical trials [61].

Thiophene: Thiophene is a five-membered heteroaromatic ring with sulphur and their chemical formula is C_4H_4S, which is frequently utilized as a component in pharmaceuticals (Fig. 4). Its metabolism can result in the creation of reactive metabolites, it is regarded as a structural warning [62]. The synthesis of the highly reactive electrophilic thiophene metabolites *i.e.* thiophene S-oxides and thiophene epoxides are cytochrome P450-dependent [63,64]. These reactive metabolites with thiophene bases are frequently to account for drug-induced hepatotoxicity

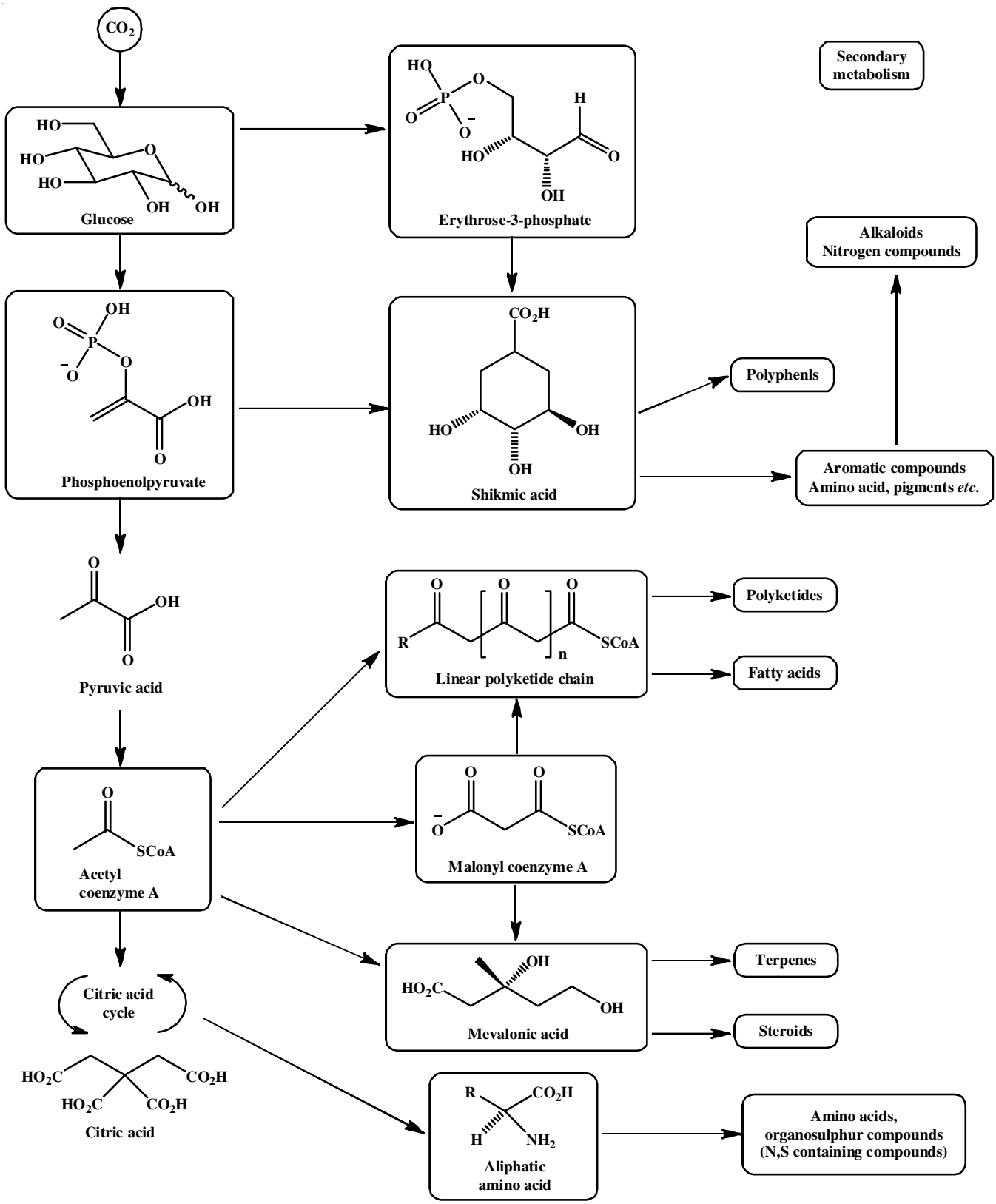


Fig. 3. Synthesis of phytochemicals from secondary metabolites adopted from Clayden [49]

also [65]. With an IC_{50} value of 58 µM, comp-ound **49** exhibited encouraging inhibitory activity against HIV-1 protease but no activity against HIV-1 integrase [66]. It is interesting that comp-ound **44** showed no effect in the presence of visible light or in the dark, but showed a dose-dependent inhibitory activity against HIV in the presence of UV-A light (320-400 nm). But compound 44 showed no effect against either coxsackievirus or poliovirus [67]. Thiophene[3,2-*d*]pyrimidine was discovered

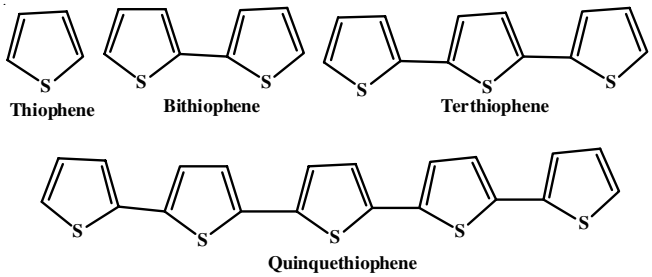


Fig. 4. Structures of thiophene compounds

to be a potential scaffold in Wang *et al.* [68] earlier's work when looking for extremely effective HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs). Further, they created a number of thiophene[3,2-*d*]pyrimidine derivatives with altered linkers between the core and the right wing, synthesized them and physiologically assessed them. Excellent HIV-1 inhibitory efficacy was demonstrated by a few of the synthesized compounds, some of which had low (double-digit) nanomolar (nm) 50% effective concentration (EC_{50}) values [69]. Thienopyridine derivatives' antiviral impact on Mayaro virus' replication *in vitro* was first demonstrated by Amorim *et al.* [70] indicating the possibility of using these compounds as antiviral agents against alphaviruses.

Polyenes: A type of *Streptomyces* bacterium produces polyenes, a class of broad-spectrum antifungal substances with a cyclic amphiphilic macrolide substructure [71]. The polyenes' propensity to bind to ergosterol, a common steroid found in fungal cell walls, renders them antifungal. This depolarization of the membrane causes increased K^+ and Na^+ permeability, which in turn causes cell death [72]. Amphotericin B (AmB, 1), a polyene medicine, is the primary medication used to treat fungal infections. Other substances in this class include nystatin (2) and natamycin (3) as shown in Fig. 5 [73]. In previous study [74], in cultured BHK-21 cells, it has been demonstrated that amphotericin B enhances the inhibitory impact of acyclovir on the reproduction of pseudorabies virus (PRV). The function of the macrolide structure has been investigated in relation to the potentiation of the antiviral activity of acyclovir by polyene macrolide antibiotics by Malewicz *et al.* [75]. A big and stiff macrolide ring seen in polyene macrolide antibiotics was linked to acyclovir potentiating effect (amphotericin B and aureofacin). Pimaricin and filipin, two polyene antibiotics and nystatin A1 and lienomycin, two polyene antibiotics with large but flexible macrolide rings, did not potentiate the antiviral action of acyclovir [75].

Alkaloids: About 15 to 20% of all vascular plants have alkaloids (Fig. 6). Plants produce them from the amino acids [76]. The *in vitro* activity against polio type III and vaccinia viruses of 36 alkaloids derived from *Catharanthus roseus* or *C. lanceus* was examined [77,78]. Pericalline, the most effective of these nine alkaloids as an antiviral, was the most effective [79,80]. Houghton *et al.* [81] evaluated several naturally occurring chromone alkaloids (produced from the rootbark of *Schumanniophyton magnificum*) for suppression of HIV and HSV infections in C8166 and Vero cells, respectively, in an effort to link the structure with the antiviral action. For screening,

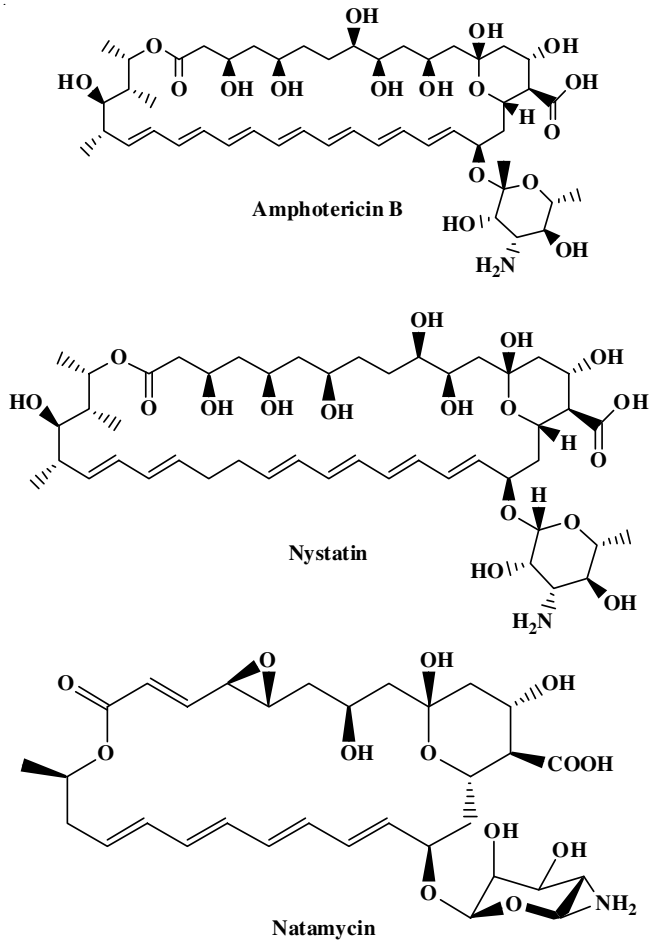


Fig. 5. Diagram showing various antibiotics (polyenes)

the authors additionally synthesized acyl and methyl derivatives. It was discovered that the compounds' free hydroxyl groups and piperidine ring appeared to favour their anti-HIV action. The anti-HIV activity was believed to be caused by irreversible binding to gp 120 [81]. The impact of berberine alkaloid on IAV infections was investigated *in vitro*. While berberine's IC_{50} was 0.01 M, it can reduce IAV type A/PR/8/34 in RAW-264.7 cells at concentrations of above 1 M. A different strain of H1N1 IAV was likewise inhibited from growing *in vitro* by this alkaloid, with an IC_{50} of 0.44 µM [82]. A different research team [83] discovered the alkaloid homonojirimycin (HNJ), which was tested for its antiviral activity against the IAV/PR/8/34 (H1N1) strain. With an inhibitory concentration EC_{50} of 10.4 µg/mL, HNJ demonstrated significant antiviral activity against IAV. Özçelik [84] showed that alkaloids of numerous types show good antiviral activity against HSV-I in the MDBK cell line. It is plausible to draw the conclusion that these compounds have a strong potential for development as antiviral drugs against these infectious viruses given the effectiveness of these antiviral alkaloids in various experimental models. However, a deeper comprehension of their pharmacological characteristics and clinical results is necessary before these alkaloids and their derivatives can be employed as antivirals [84].

Saponins: Saponins are naturally occurring glycosides with surface activity that have a particular foaming property (Fig. 7). The soapwort plant (*Saponaria*), whose roots were

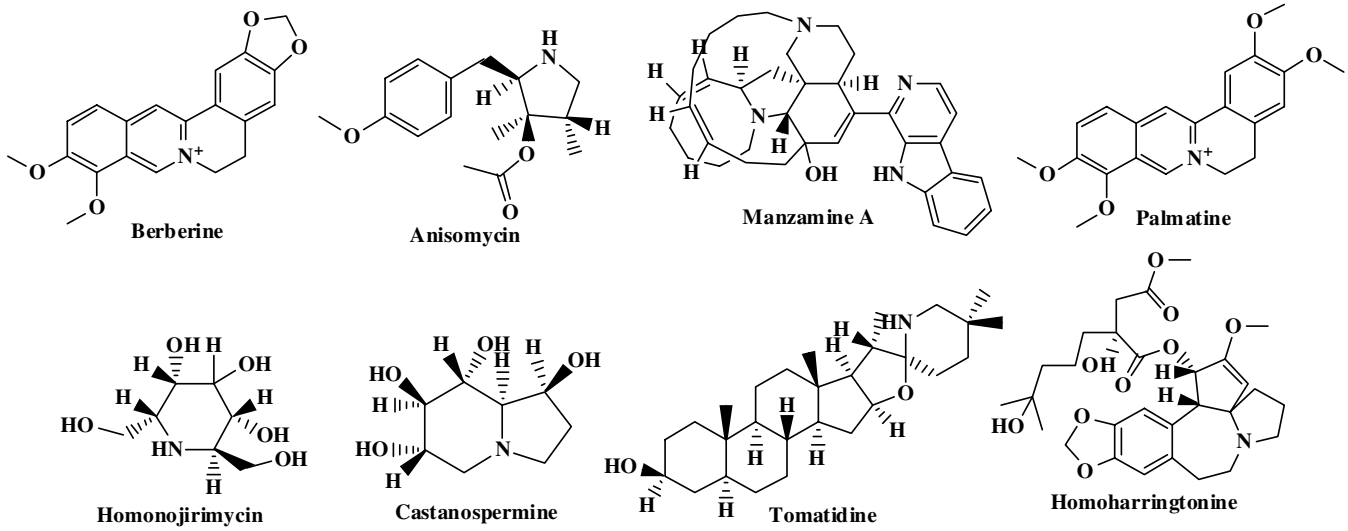


Fig. 6. Illustration of several types of active biological alkaloids

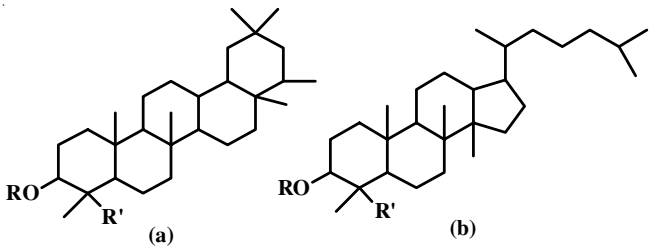


Fig. 7. Different types of saponins

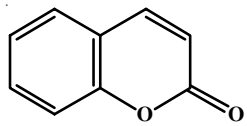


Fig. 8. Structure of coumarin

once used as soap, gave them their name despite the fact that they are mostly produced by plants, lower marine creatures and some bacteria (Latin sapo means soap) [85]. The capacity of saponins to foam is enhanced by the combination of hydrophobic or fat-soluble sapogenin and hydrophilic or water-soluble sugar component. Triterpenoid saponins are occurs naturally sugar-triterpene conjugates that have a variety of biological properties, including antiviral activity. The replication of the herpes simplex virus type 1 was evaluated against two compounds derived from natural sources. They failed to exhibit any cytotoxicity during the antiviral test conditions. The herpes simplex virus type 1 DNA synthesis was suppressed by the triterpenoid saponin (s21), which was isolated from a Brazilian plant and belongs to the oleanane group. The ursane group triterpenoid saponin (s17), which was discovered from a Chinese plant, seems to prevent the formation of the viral capsid protein in herpes simplex virus type 1 [86]. Purified saponin combination from *Maesa lanceolata* is one example of a saponin and sapogenin that can inactivate viruses. By inhibiting HIV-1 protease activity, triterpenoid sapogenin oleanolic acid suppresses HIV-1 virus replication [87].

Coumarins: The most abundant sources of coumarins are still plants in the Rutaceae and Umbelliferae families (Fig. 8). Angelica and peucedanum species were the subjects of the majority of the phytochemical research [88]. Coumarins, often referred to as 1,2-benzopyrones, are a significant class of low-molecular weight phenolics that have been successfully utilized to treat and prevent a wide range of diseases. Various plant sources contain a group of natural substances known as coumarins [89].

Some of the isolated coumarins displayed intriguing biological properties. For instance, psoralidin and decursin from *Psoralea coryfolia* both exhibit toxicity against various human cancer cell lines [88]. The coumarins have anti-inflammatory, antioxidant, anticancer, antiviral, anticoagulant and other properties. They have fantastic medicinal potential as a result. Due to the many kinds of substitutions in their fundamental structure, the coumarins have varying structures that can affect the biological activity of these compounds [89].

Coumarins (benzopyrones) are regarded as a favoured structure for creating innovative antiviral medicines with high affinities and specificities to various molecular targets. Due to the lactone group's role as a facilitator of protein-ligand interaction and the coumarins' special pharmacophore of a planar aromatic nucleus coupled to a hydrogen bond acceptor. In the past three decades, coumarins have drawn enormous attention as possible orally accessible non-peptidic antiviral medicines. Recently identified lead compounds with coumarin scaffolds are in various stages of therapeutic development and include natural, semi-synthetic and synthetic forms. Even though several assessments from the past have already been released, they have all notably emphasized the anti-HIV potential of derivatives of coumarins [90].

Many coumarins have been discovered to block various phases in the HIV replication cycle. Numerous plant-derived substances have been tested for inhibitory actions against HIV replication. Numerous coumarins have been demonstrated to block the reverse transcriptase of a number of retroviruses, including HIV, *in vitro* [91].

Polyphenolics: The term "phenolic compounds" refers to a broad class of molecules that include both those with a single phenol ring, such as phenolic acids and phenolic alcohols and

those with a polyphenol structure (*i.e.*, many -OH groups on aromatic rings) (Fig. 9) [92,93]. The amount of phenol rings a polyphenol contains and the structural components that hold those rings together are used to classify polyphenols into a number of different groups [94]. Typically, polyphenolic compounds are described as a varied category of naturally occurring chemicals with numerous phenolic functions. They are distinguished structurally by the presence of one or more aromatic rings with six carbons and two or more phenolic hydroxyl groups, which are attached directly to the aromatic ring. Although mono-phenols like *p*-coumaric acid are technically not polyphenolics, they share many of their features and traits and are best thought of as functional polyphenolics. Polyphenol is divided into five main categories [95]. Higher plants frequently contain these substances. They are useful for synthetic, medical and industrial purposes. It is known that polyphenols found in nature have a wide range of biological functions. In diseases including AIDS, cardiac conditions, ulcer development, bacterial infection, mutagenesis and brain abnormalities, they are discovered to be promising candidates for use as medications [96]. Some polyphenols are curcumin, ellagic acid, tannic acid, *etc.*

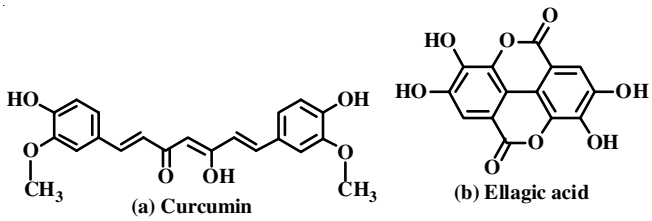


Fig. 9. Illustration of some of the naturally available polyphenols

The primary classes with antiviral activity against a broad range of virus families, including retroviridae, hepadnaviridae, hespervirides, HIV virus, polio virus, diarrhoea virus, *etc.*, are polyphenols and bioflavanoids. One of the main classes of polyphenols are bioflavanoids, which have potent antiviral properties like quercetin, kaempferol and rutin. It has been discovered that flavonols are more effective than flavones in fighting HIV and type-1 herpes simplex virus. Additionally, flavonoids and other antiviral substances have been shown to work in harmony. Acyclovir and 5-ethyl-2′-dioxyuridine, for instance, have greater anti-HSV and anti-pseudorabies activity when quercetin is present. Additionally, apigenin increases the effectiveness of acyclovir's antiviral activity against these viruses [97,98].

Sulphides: Sulfur is essential for life and molecules containing sulphur are significant in cellular biochemistry (Fig. 10). Foods contain a variety of naturally occurring organosulfur compounds. They can be found in cooked meat and fish as well as vegetables, particularly allium vegetables. These organosulfur compounds are abundant in garlic, onion and leeks. A lot of artificial food tastes employ the organosulfur chemicals. They influence how food tastes and smells. The flavour and fragrance of garlic are attributed to diallyl disulfide and diallyl sulphide, which make up 66% and 14% of the oil, respectively. Since ancient times, the medicinal benefits of the organosulfur compounds found in garlic and onions have been known. For thousands of years, India, China and Egypt have used onion

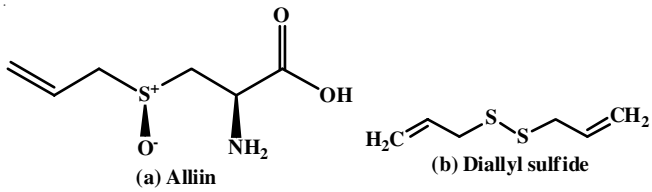


Fig. 10. Diagram showing various sulphides

and garlic as folk remedies. They have been employed as astringents, antibiotics and antithrombotics. Their long-term and excessive intake, which could make them hazardous, has been motivated by their positive health effects. Only a few of the numerous organosulfur compounds found in natural foods have had their toxicity evaluated [99].

Garlic and onions have a high concentration of organosulfur compounds, which is primarily responsible for their biological characteristics. The cysteine sulfoxides and γ-glutamylcysteines are the two most significant organosulfur compounds in alliums [100].

Furthermore, plant extracts have demonstrated broad-spectrum action against drug-resistant viruses, which may be related to the large number of multifunctional components found in plants. Based on the virus strains and various stages of viral life cycle, such as viral entry, fusion, replication, assembly and interactions with certain hosts, these extracts' or their purified constituents' antiviral effect may manifest in a variety of ways. For thousands of years, people have used garlic as a culinary ingredient, condiment and spice as well as a traditional remedy for a variety of illnesses, including viral disorders. Alliin (S-allyl-L-cysteine sulfoxide) is the most abundant sulfur compound found in fresh as well as dry garlic (10-30 mg/g). Allicin itself is very unstable and can be decomposed *in vitro* into other organosulphur compounds (OSCs) including diallyl disulfide (garlicin or DADS), diallyl sulfide (DAS), diallyl trisulfide (allitridin or DATS) andajoene and vinyl-dithiins. Garlic extract (GE) and its OSCs have demonstrated antiviral effectiveness in pre-clinical studies (*in vitro* and *in vivo*) against a variety of viral illnesses, including the flu and respiratory infections [101].

Lignans: The kingdom of plants is abundantly home to lignans, long recognized as natural compounds (Fig. 11). In this broad class, more than 200 different compounds have been found and it is clear that there is a wide range in the chemical assembly of the two distinctive phenylpropanold units, as well as in the level of oxidation and kinds of substituents. Natural product chemists continue to describe novel lignans and their variety and range of occurrence in the plant world are both fields of study that are constantly growing [102].

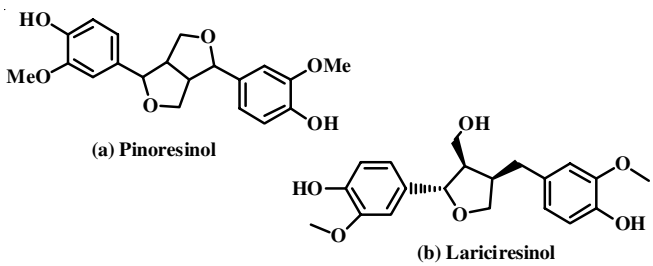


Fig. 11. Chemical structure of plant-derived Lignans

Pinoresinol, lariciresinol, syringaresinol, medioresinol and sesamin (SES, a lignan precursor) are the plant lignans of particular relevance. The two enterolignans (mammalian lignans) enterodiol and enterolactone are generated from plant lignans in the large bowel [103]. The term "lignans" refers to a group of secondary metabolites that form when two or more phenylpropanoid units undergo oxidative dimerization. Despite having similar biosynthetic origins, they have a wide variety of structural forms. Furthermore, it is widely known that this group of substances exhibits a variety of strong biological activity. Liu *et al.* [104] isolated three new dibenzocyclooctadiene lignans, heilaohulignans A-C, from Heilaohu, the roots of Kadsura coccinea, used as a treatment therapy for rheumatoid arthritis and gastroenteric disorders [104]. New lignans are continually being discovered particularly Heilaohulignan C showed cytotoxic effects in a variety of human cancer cell types [105].

The Chinese term for the root of *Isatis indigotica* Fort is *Radix isatidis*, also known as Banlangen. *Radix isatidis* containing traditional Chinese medicine items were once out of supply in China during the SARS outbreak in year 2003. Numerous compounds with lignans structure have so far been identified from *Radix isatidis* and they have shown to have antiviral properties [106].

Terpenoids: All living things contain a group of chemicals known as terpenoids (Fig. 12). However, compared to other living things, green plants and flowering plants in particular, demonstrate an abnormally large amount of terpenoids, both per species and overall [107].

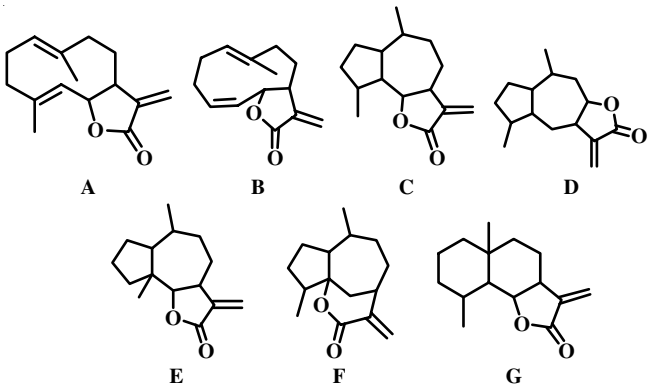


Fig. 12. Structures of some sesquiterpene lactones: A: Germacranolides, B: Heliangolides, C+D: Guaianolides, E: Pseudoguaianolides, F: Hypocretenolides, G: Eudesmanolides

Terpenoids are a group of organic compounds made up of many isoprene (C5) structural units that are produced from mevalonic acid (MVA). Terpenoids are abundant in nature and come in a variety of shapes and forms. Over 50000 terpenoids have been discovered in nature to this point, 1 and the majority of them are isolated from plants. Gibberellin and carotenoids are examples of terpenoids that have a significant impact on the growth and development of plants. For spices, flavourings and cosmetics, many volatile terpenoids are used as raw materials, including menthol and perillyl alcohol. Terpenoids can also have significant economic importance. They are utilized as industrial raw materials, pesticides and other things, such pyrethrin and limonoids. Humans first became aware of some terpenoids' biological activities in 1960s, but not all terpenoids. By 1970s, research on the biological effects of terpenoids had begun to pick up speed and had reached its first minor peak [108].

Sesquiterpene lactones are C15 terpenoids, which constitute a class of secondary metabolites. Three isoprene units are used to create them. A portion of the isoprene group in one of their methanol groups was oxidized to lactones. A semi-synthetic derivative of artesunate was evaluated for its antiviral properties. It has been demonstrated that artesunate inhibits the replication of human cytomegalovirus (HCMV), herpes simplex virus type 1 (HSV-1), epstein-barr virus and human herpes virus 6A in *in vitro* conditions, whereas artemisinin is inactive against human herpes virus 6A and acts only weakly against HCMV. This demonstrates that artesunate is more effective at combating herpes viruses than artemisinin. While artemisinin exhibits anti-HCV(HCV hepatitis C virus) action, artesunate also exhibits anti-HBV activity (HBV-hepatitis B virus) [109].

Flavonoids: A large class of polyphenolic compounds known as flavonoids is primarily found in fruits, vegetables, seeds, flowers and beverages (Fig. 13). Diphenylpropane (C6-C3-C6), a natural flavonoid with two aromatic rings at each corner and a three-carbon ring in the middle, has the chemical moiety C6-C3-C6. Natural flavonoids' most well-known biological actions are hormone action, cardio-protection, bone resorption inhibition and cancer prevention. Anthocyanidins, flavanones, flavanols, flavones and isoflavones are six categories of natural flavonoid chemicals [110].

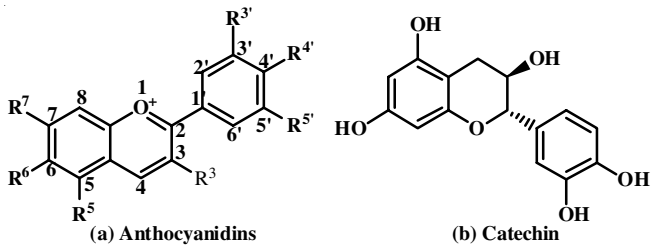


Fig. 13. Diagrams of some naturally available flavonoids

Coronaviruses were resistant to the antiviral and immunomodulatory effects of flavonoids. As a result, the antiviral abilities of flavonoids may also be useful in the ongoing COVID-19 epidemic. By inhibiting 3C-like protease ($3CL^{pro}$), which is capable of obstructing the enzymatic activity of SARS-CoV $3CL^{pro}$, certain flavonoids' antiviral activity against coronaviruses (CoVs) is identified [111]. There are various ways that flavonoids, which are phytochemicals, inhibit and interact with viruses. They can prevent viral attachment and entry into cells, interfere with various viral DNA replication phases, translate proteins and process polypeptides. Additionally, they can stop the viruses from spreading and invading other healthy host cells [112].

Conclusions

Several medicinal plant species have been reported to treat a wide range of viral infections. Phytochemicals such as alkaloids, terpenes, polyphenols, quinones, flavonoids, lignins, saponins,

steroids, tannins, coumarins and thiosulfonates were identified to be major bioactive compounds in medicinal plants, which have been showed significant results to control viral diseases. These secondary metabolites have showed potential inhibitory results against AIDS, HBV, dengue, chikungunya, HCV, HSV, influenza virus, SARS-CoV-2 and other viruses. Moreover, *in silico* and *in vitro* studies have shown effective use of phytochemicals for the treatment of viral infections. Therefore, the combination of phytochemicals with the synthetic compounds or any other drug could be effective approach to discover the good antiviral therapies. The antiviral therapies for the life-threatening viral diseases are very expensive and have adverse side effects. Thus, the approach using the phytochemicals could be better alternative in the development of antiviral compounds. However, more research on different biodiversity-rich regions can be investigated to obtain more effective potent phytochemicals and their metabolites as antiviral agents. To create new derivatives of current phytochemicals, the contribution of computational methods should also be assessed. Studies conducted *in vitro* and *in vivo* should be used to further validate such *in silico* work. To distribute and target certain infected cells, synthetic derivatives and nano-formulations are required.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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