Antivirals: Past, Present and Future

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Abstract

The uses of antiviral agents are increasing in the new era along with the development of vaccines for the effective control of viral diseases. The main aims of antiviral agents are to minimize harm to the host system and eradicate deadly viral diseases. However, the replications of viruses in host system represent a massive therapeutic challenge than bacteria and fungi. Antiviral drugs not just penetrate to disrupt the virus' cellular divisions but also have a negative impact on normal physiological pathways in the host. Due to these issues, antiviral agents have a narrow therapeutic index than antibacterial drugs. Nephrotoxicity is the main adverse reaction of antiviral drugs in human and animals. In this chapter, we summarize the antiviral agents' past, present and future perspectives with the main focus on the brief history of antiviral in animals, miscellaneous drugs, natural products, herbal and repurposing drugs.

Keywords

Virus · Therapy · Bacteria · DNA · RNA

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22.1 Prologue

Vaccine development has long been the first and foremost approach in the control of viral diseases (Saminathan et al. 2016). However, with the development of the first human antiviral drug, idoxuridine, and its later approval in 1963, a new era of antiviral treatment development began (De Clercq and Li 2016). Because of viral replication cycle, which involves usage of host cell biochemical machinery, antiviral drugs can also affect the function of the host's pathways resulting in the great risk of toxicity. Therefore, the major concern in antiviral drug development is the identification of specific targets with increased selectivity and reduced side effects, which limit the therapeutic use of antiviral drugs in comparison to antibacterial agents (Dal Pozzo and Thiry 2014). In the early 1900s, state-of-the-art review articles on antiviral chemotherapy in veterinary medicine listed several drawbacks of low antiviral drugs use in veterinary medicine. Those included usage restricted to a single virus and specific animal species, problems with high spectrum activity and low cytotoxicity, high costs of development of new chemical compounds and absence of rapid diagnostic techniques allowing prompt use of a specific antiviral agent in the course of an acute infection (Rollinson 1992a, b). Most of the antiviral drugs used in animal medicine have been originally developed against human viral infections and their clinical use in veterinary medicine is not widespread and common. Nevertheless, several licensed human antiviral agents are being used with cascade principle for treatment of animal diseases (e.g. acyclovir, idoxuridine and trifluridine against feline herpesvirus-1 ocular infection in cats) (Thiry et al. 2009). Currently, the only licensed antiviral drug in veterinary medicine is feline interferon-omega (IFN-ω), whose mechanism of action involves a combination of antiviral and immunostimulatory activity (De Clercq and Li 2016; Bracklein et al. 2006). Most antiviral agents interfere with the synthesis or regulation of viral nucleic acids (Fig. 22.1) and act by nucleoside analogues that block elongation of newly synthetized DNA or RNA chain. Other antiviral agents used in veterinary medicine act as neuraminidase (oseltamivir) or amino acid (L-lysine) inhibitors, while novel treatment options such as small inhibitory RNAs are also under investigation (Dal Pozzo and Thiry 2014; Sykes 2013). In recent years, the use of antiviral agents in veterinary medicine has become more favourable with growing interest in its research. This is partially due to successful outcomes of antiviral therapy in some human diseases and partially due to advances in internal veterinary medicine with the development of novel and sophisticated diagnostic and treatment protocols. In addition to that, current measures for control of viral infections such as vaccination or removal of infected animals from breeding stock by culling have many limitations. Therefore, antiviral agents represent a promising alternative for the treatment of viral diseases in veterinary medicine (Dal Pozzo and Thiry 2014).

One of the most common approaches in antiviral drug discovery is rational drug design, which is based on the understanding of the structures and functions of target molecules. It comprises three steps of drug design: (1) identification of the receptor or enzyme relevant for the disease that the drug is being developed for, (2) discovery of the structure and function of the receptor or enzyme of interest and (3) use of the

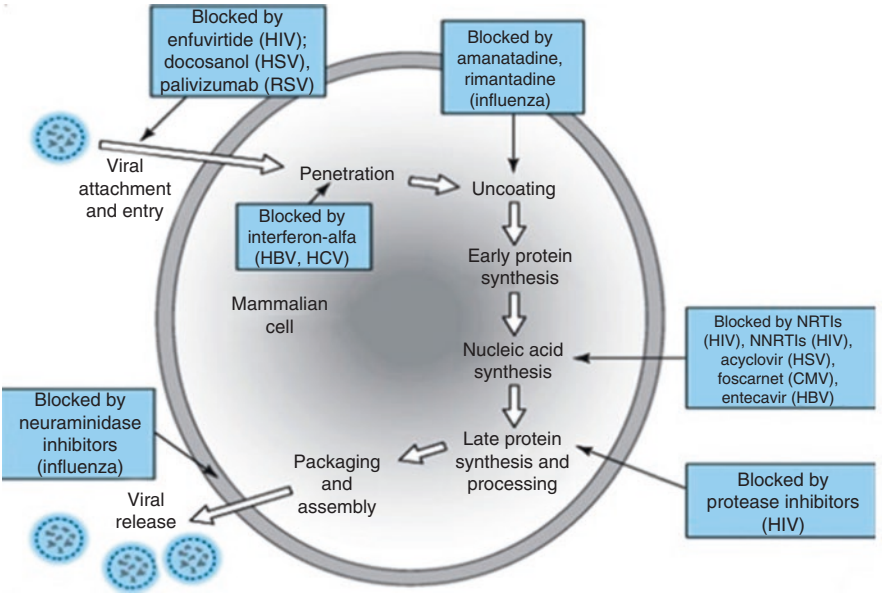


Fig. 22.1 Possible general mechanism of action of antivirals

information from step 2 in order to design a drug molecule that would interact with the receptor or enzyme in a therapeutically beneficial way. The best known example of this approach is azidothymidine (AZT), used in the treatment of human immunodeficiency virus (HIV), which acts by inhibiting HIV reverse transcription. Interestingly, it was originally developed to target reverse transcription of avian retroviruses that may cause cancer and was later successfully applied to HIV as well (Olivero 2018). The other widely used approach is high-throughput screening (HTS) methods, which enable validation of a number of biological modulators against a chosen set of defined targets. They yield rich data sets over a short span of time by combining expertise in liquid handling and robotic automation, multiplatform plate reading and high-content imaging. The number of thus emerged "active hits" is normally around 2% of the total number of potential biological modulators screened. Steps in HTS pipeline can be summarized as follows: (1) sample preparation, (2) sample handling and (3) readouts and data acquisition. The most common HTS methods are targeted/selected screens, diversity and high-content screens and RNAi screens (Szymański et al. 2012). Targeted or selected screening is based on identification of compounds that can selectively inhibit or bind to a specific protein of interest. If the crystal structure of the protein of interest is known, it is usually done by in silico three-dimensional (3-D) modelling, while if the ligand for the protein of interest is known, software can search libraries for the other compounds with similar characteristics and binding properties. Examples of such approach include identification of compounds against HIV, filoviruses, poxviruses, arenaviruses, etc. (Marriott et al. 1999). Another commonly used screening method is

diversity screening, based on identification of compounds that inhibit viral replication or pathogenesis at any level. This approach involves a much broader target base, instead of focusing the screening against one specific protein of interest. It has been applied in the identification of candidate small-molecule inhibitors against dengue virus, yellow fever virus and New World arenaviruses (Valler and Green 2000). High-content screening (HCS) is a subclass of diversity screening method developed upon automation of cellular imaging and analysis techniques. It allows imaging multiple cells at the same time and measurement of multiple parameters, such as shape, texture, staining localization and intensity, total number of cells, size of the nucleus and percentage of virus-positive cells (Brodin and Christophe 2011). Another type of screening for antiviral drug discovery is RNAi screens. siRNAs incorporate into the RNA-induced silencing complex and bind to the target mRNA, thereby inducing degradation of the mRNA and thus preventing its translation into a protein. shRNA, on the other hand, silences protein by forming a "short hairpin" loop through folding back upon itself. Genome-wide RNAi screens have been used to study the pathogenesis of HIV, influenza virus, West Nile virus, Ebola virus, etc. (Hirsch 2010). In addition to the above-mentioned methods, recent advances in genomics, bioinformatics and associated technologies offer new opportunities in antiviral drug discovery. Computational methods enabled construction of databases that contain information related to biological function, chemical structure, biologic activity and many other properties of potential antiviral compounds that can all contribute to identification of new lead bioactive species (Prichard 2007).

22.2 Vidarabine

Vidarabine (9-d-arabinofuranosyl adenine) was the first antiviral agent licensed for systemic treatment of herpes viral infections in humans (Fenner et al. 2014). It is an adenosine analogue that is converted by cellular enzymes to its active intracellular derivate, vidarabine triphosphate. Obtained triphosphate form further acts as competitive inhibitor of both viral and host DNA polymerase, where viral enzymes are much more susceptible to the drug than that of the host cell (Sykes 2013; Schaechter 2010). However, independence on viral thymidine kinase-mediated phosphorylation results in greater host cell toxicity (Sykes 2013). It is used as a topical treatment for feline herpes keratitis, albeit in vitro studies have shown it to be less potent against feline herpesviruses than trifluridine and idoxuridine (Nasisse 1990). In vitro activity has also been demonstrated against feline end equine rhinopneumonitis (Ayisi et al. 1980). Five to six times daily administration as a 3% ophthalmic ointment was reported to be well tolerated by cats and effective in the treatment of feline keratoconjunctivitis sicca. It has also been reported to be effective against idoxuridine-resistant strains (Sykes 2013; Stiles 1995).

22.3 Acyclovir

Acyclovir (acycloguanosine) is an acyclic analogue of the purine nucleoside deoxyguanosine that has been widely used to treat herpesvirus family infections (Sykes and Papich 2013; Perazella and Shirali 2014). The activation involves phosphorylation of the drug firstly by virus-encoded thymidine kinase enzymes into monophosphate form, followed by further phosphorylation to triphosphates by host cell enzymes (Sykes and Papich 2013). Acyclovir triphosphate is a better substrate to viral than host DNA polymerase, resulting in its concentration in infected cells. Due to the lack of 3′-hydroxyl group, the drug inhibits viral DNA polymerase enzyme, as upon its incorporation further DNA chain elongation is disabled (Sykes and Papich 2013; Salvaggio and Gnann 2017). Hence, as a therapeutic, it is mostly used to treat DNA virus infections, in particular herpes simplex virus types 1 and 2 and varicella-zoster virus (Salvaggio and Gnann 2017). In animal medicine, it has been primarily used against feline herpesvirus-1 (FHV-1) infections, but not as efficiently as against the same human virus in vitro, which is related to its low oral bioavailability in cats (Maggs and Clarke 2004; Gaskell et al. 2007; Nasisse et al. 1989). The acyclovir prodrug valacyclovir shows better pharmacokinetic properties in terms of its enhanced bioavailability, resulting in faster absorption after oral administration upon which it gets rapidly metabolized to acyclovir. Acyclovir and entecavir had the ability to block nucleic acid synthesis (Fig. 22.1). However, administration of valacyclovir as well as subsequent increased plasma acyclovir concentrations has been associated with adverse effects, such as nephrotoxicity, myelosuppression and renal and hepatic necrosis, and yet was not effective against FHV-1 infection (Nasisse et al. 1989). These findings suggest systemic administration of neither acyclovir nor valacyclovir is recommended for treatment of herpesvirus infections in cats. Ganciclovir, another purine nucleoside analogue that resembles acyclovir and is widely used to treat cytomegalovirus infections in human medicine, has been shown to be more effective against FHV-1 in vitro, but unfortunately there is lack of data on its efficacy and safety in animals (Sykes 2013). On the other hand, topical acyclovir treatment was shown to be effective against FHV-1 conjunctivitis and keratitis when applied at least 5 times a day and did not produce toxic effects (Williams et al. 2005). Apart from cats, the existing studies provide data on acyclovir treatment in horses, where intravenous administration resulted in 9,6-hour half-life, contrary to very low oral absorption (< 3%) (Williams et al. 2005; Riviere and Papich 2013). It has therefore been suggested that IV treatment could be administered twice daily for equine herpesvirus-1 (EHV-1) (Riviere and Papich 2013). In birds, oral treatment with 120 mg/kg of acyclovir every 12 h has been shown as the minimum dose necessary to maintain concentrations that exhibit antiviral effect in pheasants (Rush et al. 2001). Studies in dogs report oral absorption of acyclovir of 80–90%, but it becomes saturated at high doses (de Miranda et al. 1981).

22.4 Penciclovir

Penciclovir [9-(4-hydroxy-3-hydroxymethylbut-1-yl)] is guanosine analogue that resembles acyclovir in structure, mechanism of action and antiviral activity spectrum. Comparing to acyclovir, penciclovir-triphosphate accumulates in virus-infected cells in much higher concentrations and for longer half-life (10–20 times longer than acyclovir) (Salvaggio and Gnann 2017; Gill and Wood 1996). However, it is less potent than acyclovir triphosphate as it exhibits lower affinity for viral DNA polymerase enzyme, which would allow lower and less frequent dosage in clinical use. In vitro studies have proven its efficacy against FFHV-1 virus and hepatitis B virus (Dannaoui et al. 1997; Shaw et al. 1994; Korba and Boyd 1996). Because of penciclovir's poor oral bioavailability (<5%), famciclovir was developed as the oral formulation (Salvaggio and Gnann 2017). The use of penciclovir will be further described along with famciclovir.

22.5 Famciclovir

Famciclovir (the diacetyl ester of 6-deoxy-penciclovir) is the oral prodrug of acyclovir with the improved bioavailability which, following oral administration, gets rapidly converted to its active metabolite penciclovir by di-deacetylation and oxidation. However, the pharmacokinetics of penciclovir and famciclovir in cats appears to be nonlinear (saturable) and absorption variable compared to other species. This is supported by the observation that administration of the same doses of famciclovir to cats and other species resulted in much lower plasma concentrations and longer time required to reach peak plasma concentrations in cats (Thomasy et al. 2007). Thus, limited famciclovir metabolism stems from deficiency of hepatic aldehyde oxidase enzyme in cats, which converts famciclovir to its active form (Dick et al. 2005). Even though famciclovir has to be administered in high oral doses to develop adequate plasma concentrations in cats, it seems to be well tolerated and successful in the treatment of FHV-1-associated conjunctivitis (Thomasy et al. 2007; Malik et al. 2009; Thomasy et al. 2012). Due to saturable metabolism, oral administration of both 40 and 90 mg famciclovir/kg to cats resulted in equivalent serum and tear penciclovir concentrations, implying that 40 mg/kg is equally effective against FHV-1 as the higher dose (Thomasy et al. 2012). In rats and dogs, famciclovir absorption and metabolism appear to be similar to those previously reported in people, despite the observed slower conversion of famciclovir to penciclovir in both species (Filer et al. 1994).

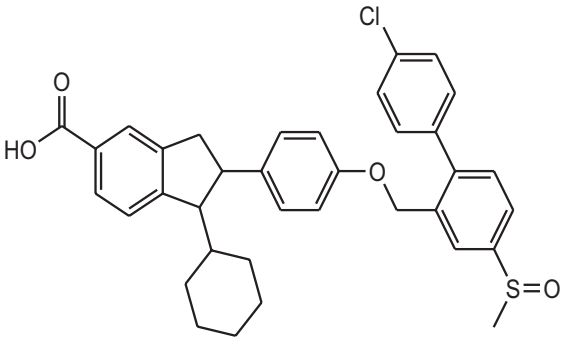
22.6 Ribavirin

As first described by Witkowski et al. in 1972, ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) is a triazole nucleoside analogue that inhibits replication of both DNA and RNA viruses by interfering with viral mRNA synthesis (Witkowski

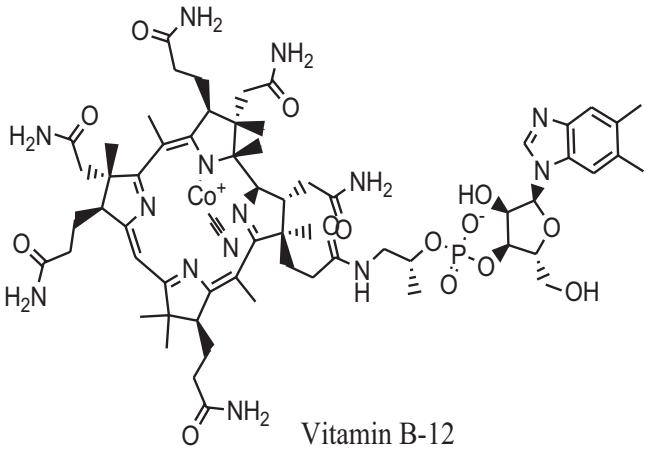
et al. 1973). It is active against a wide range of viruses including adenoviruses, arenaviruses, bunyaviruses, herpesviruses, orthomyxoviruses, paramyxoviruses, picornaviruses, poxviruses, retroviruses, rhabdoviruses and rotaviruses, but the strongest effect exhibits against influenza viruses and, in combination with interferon, against hepatitis C virus (Dolin 1985; Gustafson 1986; Te et al. 2007). It has several possible mechanisms of action. Firstly, as ribavirin monophosphate, generated by adenosine kinase-mediated phosphorylation, it can indirectly inhibit the synthesis of guanine nucleotides. Further, the phosphorylated triphosphate form competitively inhibits binding of ATP and GTP to RNA polymerase (Riviere and Papich 2013). Orally administered ribavirin has been shown to worsen the condition of cats experimentally infected with calicivirus. Toxic effects mainly resulted from drug-induced thrombocytopenia and include depression of red and white blood cells, increased alanine aminotransferase activity, icterus and body weight loss. However, observed clinical symptoms withdrew within one week after treatment discontinuation (Riviere and Papich 2013; Povey 1978). Interestingly, these side effects were not observed in dogs treated for 2 weeks with 60 mg/kg of the drug (Canonico 1985). In kittens experimentally infected with feline infectious peritonitis virus (FIPV), treatment with neither free nor liposomal ribavirin improved survival rate and, similarly to animals infected with calicivirus, resulted in intrinsic toxicity (Riviere and Papich 2013; Weiss et al. 1993). Activity of ribavirin has also been demonstrated against bovine viral diarrhoea virus, bovine herpes virus-1 and parrot bornavirus 4 in cell culture models (Glotov et al. 2004; Musser et al. 2015).

22.7 Benzimidazoles

The antiviral activity of benzimidazole nucleosides was first reported by Tamm, Folker and co-workers in 1954. They designed 5,6-dichloro-1-(β-D-ribofuranosyl) benzimidazole (DRB), which had various biological activities including antiviral activity against RNA and DNA viruses. The antiviral activity of DRB is via inhibiting cellular RNA polymerase II thus inhibiting viral and cellular RNA synthesis (Migawa et al. 1998; Porcari et al. 1998; Chen et al. 2000; Townsend et al. 1995). In pharmaceutical chemistry, heterocyclic compounds particularly the benzene-fused are of great importance. In the class of benzene-fused compounds, benzimidazole and its derivatives are known for their wide variety of biological activities. Biologically active compounds such as vitamin B12, albendazole, mebendazole and thiabendazole contain a benzimidazole nucleus in their structure (Fig. 22.2) (Shaharyar et al. 2016). Structure–activity relationship (SAR) studies show that due to a change in the group on the basic structure, benzimidazoles display a wide array of biological activities including analgesic, antibacterial, antifungal, anticancer and antiviral (Alaqeel 2017). Moreover, a range of structurally varied nonnucleoside inhibitors (NNI) of the HCV polymerases sharing the benzimidazole pharmacophore has been reported. Among these classes of compounds, JTK-003, which is an orally active benzimidazole derivative, is in its Phase I and II clinical trial stage in Japan (Tan et al. 2002; Tomei et al. 2003). Currently, a number of benzimidazole



JTK-003



Vitamin B-12

Fig. 22.2 The chemical structure of bioactive benzimidazole derivatives JTK-003 and vitamin B12

derivatives are available in the market such as omeprazole and rabeprazole used for gastric ulcers, telmisartan and candesartan for hypertension, astemizole and mizolastine for allergic rhinitis, and albendazole, oxibendazole and mebendazole for parasitosis (Wang et al. 2015). Benzimidazoles readily interact with the biopolymers of the living system due to the fact that they are bioisosteres of cellular nucleotides (Starčević et al. 2007).

22.8 Arildone

Arildone is an antiviral drug of the 4-[6-(2-chloro-4-methoxy)phenoxyl]hexyl-3,5-heptanedione class, which is active against both DNA and RNA viruses (Kuhrt et al. 1979). It is primarily suggested to be used as a broad-spectrum antiviral agent

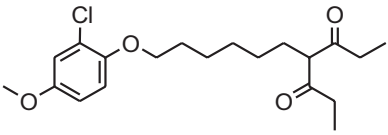


Fig. 22.3 The chemical structure of the antiviral agent arildone

because it is relatively a less toxic drug and inhibits viral replication at lower concentration (Kim et al. 1980). SAR studies demonstrated that omission of the lipophilic substituents of arildone diminished the antiviral activity (McSharry et al. 1979). Arildone (Fig. 22.3) inhibits replication of enterovirus, particularly poliovirus, via interaction with the viral capsid and hence blocking viral uncoating (Nikolaeva-Glomb and Galabov 2004). Further in vitro studies provided evidence that a direct interaction of arildone with the poliovirus capsid stabilizes the virion against heat and alkaline treatment, resulting in loss of the VP4 capsid polypeptide and blocked release of viral RNA (Fox et al. 1986). The uncoating inhibition action of arildone at lower dose can block replication of herpes virus at an earlier stage than the polymerase. Arildone is administered as a solution in dimethyl sulphoxide (DMSO) due to its poor solubility in water, and the solvent properties of DMSO may have augmented its antiviral action (Hutchinson 1985). In an animal model experiment, the ability of arildone to block the virion uncoating property to prevent paralysis and death was studied in mice intracerebrally infected with a higher dose of poliovirus type-2 (strain MEF). Moreover, IP administration of arildone suspended in gum tragacanth successfully protected the animals from paralysis and death in a dose-dependent fashion (minimal inhibitory dose = 32 mg/kg, 2X/day) (Mckinlay et al. 1982). Arildone is the first of the capsid inhibitors that demonstrated in vitro inhibition of poliovirus replication and prevented paralysis and death in poliovirus-infected mice. Such compounds with better bioactivity showed potency orally in the mouse model, even when administered days after intracerebral infection (McKinlay et al. 2014).

22.9 Phosphonoacetic Acid

Compounds consisting the carbon-phosphorous bond are rare in nature and were considered non-existent till recently. It was in 1924 that phosphonoacetic acid (PAA) was first synthesized and its antiviral activity was discovered almost 50 years later in 1973 (Shipkowitz et al. 1973). The discovery of PAA (Fig. 22.4) as an antiviral drug gave rise to intense research on its biological activities, which demonstrated PAA and its derivatives' ability to inhibit the replication of a number of viruses such as immunodeficiency, hepatitis and herpes viruses. In animal studies it was shown that PAA is active against herpes keratitis in rabbits and herpes dermatitis in mice. PAA and its derivatives being analogues of antimetabolites of pyrophosphates have their action against herpes viruses, especially in Epstein–Barr virus, CMV and HSV, through inhibiting DNA polymerase, which is important in herpes virus replication (Alimbarova et al. 2015; Overby et al. 1974). In addition, it was

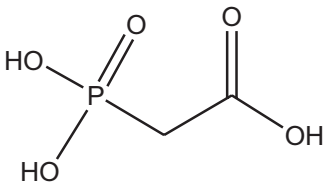


Fig. 22.4 Structure of phosphonoacetic acid

depicted in a study that polymerase activity was inhibited in lysed cultures of infected cells by PAA without affecting the enzyme in normal cells. Polymerases from both normal and infected cells were highly purified and investigated to verify their differential sensitivity towards PAA (Mao et al. 1975).

22.10 Rifamycins

Amycolatopsis rifamycinica is the first soil bacteria that provided the rifamycins in 1957. For a while, it was considered the only bacterial source of rifamycins till their discovery in *Salinispora* group. Although there are several rifamycins isolated from bacteria, the most widely used derivative of rifampicin (rifampin) is a semisynthetic rifamycin. Rifamycins are preferable as they can cross mammalian tissue and cell membrane easily (Bhattacharjee 2016). As a result, rifamycin-SV and its derivatives are deemed first line in the treatment of intracellular pathogens and demonstrated inhibitory action in various biological systems. Among the antibacterial agents of these derivatives, some act by inhibiting the bacterial DNA-dependent RNA polymerase. Furthermore, rifampin inhibits poxvirus replication in vitro via a mechanism other than inhibiting DNA-dependent RNA polymerase. In vitro screening for selective inhibition of RNA-dependent DNA polymerase (reverse transcriptase) on a number of derivatives revealed that certain derivatives prevented focus formation by RNA tumour viruses (Szabo et al. 1976). Rifamycin derivatives were also found to act against type II DNA topoisomerases. Besides, phylogenetic studies showed that viral type II DNA topoisomerase and their bacterial counterparts have similarities indicating that the antibacterial topoisomerase inhibitors can act against African swine fever (ASFV) replication. In fact, fluoroquinolones, a class of synthetic antibacterial drugs, were shown to inhibit the ASFV replication by interacting with type II topoisomerase (Zakaryan and Revilla 2016). Rifampicin, rifapentine and rifabutin (Fig. 22.5) are semisynthetic and water-soluble derivatives of 3-formylrifamycin SV, used in therapies against different Gram-positive and Gram-negative bacterial strains including methicillin-resistant *Staphylococcus aureus* (MRSA), mycobacteria (*Mycobacterium bovis* or *Mycobacterium tuberculosis*) and leprosy, legionella. They are also able to prevent viral infections (e.g. influenza) (Czerwonka et al. 2016).

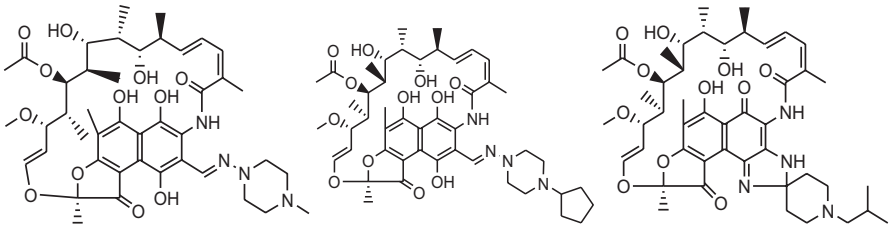


Fig. 22.5 Rifamycin-SV derivatives having antiviral activity

22.11 Other Antibiotics

The antiviral potential of antibacterial drugs has been studied on various drugs. Minocycline is among the well investigated for its actions against a number of ailments. It is a synthetic second-generation tetracycline derivative with immunomodulatory and anti-inflammatory action and widely used for the treatment of acne, rheumatoid arthritis and UTIs. Potential antiviral action of minocycline against human immunodeficiency virus, Japanese encephalitis virus and West Nile virus has been reported. It was also found promising in reducing *dengue virus* infection, with a prompt action against all the four serotypes of the virus. Minocycline generally diminished viral RNA synthesis, intracellular viral protein synthesis and thus infectious virus production. It was also found to decrease ERK1/2 phosphorylation, which is associated with intensifying pathogenesis and organ damage in *dengue virus* infection (Leela et al. 2016). Furthermore, the quinolones have showed an antiviral activity towards HIV and hepatitis C virus (HCV) in addition to their antibacterial and anticancer activity. Particularly the antimalarial drugs chloroquine and amodiaquine displayed activity against viruses like dengue virus, West Nile virus and Ebola virus by interfering with viral entry and replication (Savoia 2016). On the other hand, the compound teicoplanin isolated from an *Actinobacteria* member, *Actinoplanes teichomyceticus*, is a fermentation product that exerts bactericidal action through inhibiting bacterial cell wall biosynthesis. This semisynthetic glycopeptide teicoplanin showed a significant inhibitory activity against Ebola envelope pseudotyped viruses in Vero cells when used in the clinic. Besides, teicoplanin and other glycopeptide antibiotics, including dalbavancin, oritavancin and telavancin, but not vancomycin, had inhibitory action against the entry of Ebola virus, SARS-CoV and MERS-CoV transcription and replication-competent virus-like particles. With regard to teicoplanin's antiviral activity, various studies have reported about its action against HIV, hepatitis C virus, flaviviruses, coronaviruses, respiratory syncytial virus and influenza virus (Colson and Raoult 2016).

22.12 Several Natural Products

The world has benefited from the phenomenal discovery of penicillin by Alexander Fleming in 1928 and its development in the 1940s by Chain, Florey, Heatley and Abraham at Oxford. Similarly, the 1940s invention of important streptomycete products by Waksman, Woodruff, Schatz and Lechevalier at Rutgers University has resulted in the selective action of antibiotics against pathogenic bacteria and fungi. Ever since the invention of penicillin, microbes have played a very significant role in the discovery of newer natural product-based drugs. Currently, over 23,000 active compounds of microbial origin including antimicrobials, antivirals and cytotoxic and immunosuppressive compounds, of which 42% are made by fungi and 32% by filamentous bacteria, the actinomycetes, are available (Demain 2014). Cyclosporin 72, which is a fungus-derived potent immunosuppressant that acts through inhibition of cyclophilin, is found to have antiviral activity. Nevertheless, its immunosuppressive and calcineurin-related side effects have made it impossible for use as an antiviral agent. Therefore, continued search for structurally related cyclosporin analogues with minimal immunosuppressive activity and strong cyclophilin inhibitory action resulted in its derivative NIM 811 73. On the contrary, NIM 811 73 had 1700 times less immunosuppressive activities than cyclosporin 72 with a lesser toxicity profile and has demonstrated to possess anti-HIV and HCV activity. NIM 811 73 has passed evaluation in Phase I trial for the treatment of HCV (Butler 2008). Even though majority of natural products have been produced from terrestrial environments, marine organisms have also contributed quite a large number of bioactive compounds. Between 2000 and 2003, about 129 bioactive compounds have been isolated from marine microbes only. Various compounds with anticancer, antibacterial, antiviral, immunomodulatory and protease-inhibition activities have been isolated from marine cyanobacteria. Marketed marine products include cytarabine (Cytosar) for non-Hodgkin's lymphoma, the antiviral vidarabine (Vira-A), ziconotide (Prialt) and trabectedin (Yondelis) (Demain 2014).

22.13 Herbal Antiviral

The history of herbal drug use is widespread in both developed and developing countries, and they are still utilized because of several reasons such as fewer side effects, relatively less expensive, patient tolerance and acceptance due to long history of use (Vermani and Garg 2002). Veregen (polyphenon E ointment), which is a green tea leaf extract and a mixture of catechins, was the first herbal remedy to obtain FDA approval in 2006 for treating genital warts. Additionally, a perennial herb *Glycyrrhiza glabra* has been in use for over 20 years in Japan for treatment of hepatitis. Its dried and processed root *licorice* has a unique odour and sweet taste. Various studies have investigated the pharmacological activity of licorice against viral hepatitis. A randomized controlled trial conducted on *Glycyrrhiza glabra* derived compound glycyrrhizin and its derivatives demonstrated diminished hepatocellular damage in chronic hepatitis B and C (Fiore et al. 2008). The herb

Caesalpinia pulcherrima Swartz (Leguminosae) is a common medicinal plant in Taiwan. Its flower contains a number of metabolites like lupeol, lupeol acetate, myricetin, quercetin and rutin. Quercetin has been reported to have activity against bacteria, fungi and viruses [human immunodeficiency virus (HIV), poliovirus, herpes simplex virus (HSV)], indicating that it can be a potential antibiotic. Furthermore, rutin has also been stated to inhibit replication of parasites, bacteria, fungi and viruses (rotavirus and HSV) (Chiang et al. 2003). On the other hand, in China and Taiwan, *Ocimum basilicum* is widely used traditionally against a number of infections. A number of compounds have been reportedly found from *Ocimum basilicum* including monoterpenoids (carvone, cineole, fenchone, geraniol, linalool, myrcene and thujone), sesquiterpenoids (caryophyllene and farnesol), triterpenoid (ursolic acid) and flavonoid (apigenin). In particular, ursolic acid was shown to have inhibitory activity against herpes simplex virus (HSV)-1 and human immunodeficiency virus (HIV), as well as tumour growth (Chiang et al. 2005).

22.14 Repurposing of Drugs

Drug repurposing (or drug repositioning) is the method of assigning a new medical indication for an existing drug. The repositioned drug might be currently on the market for other medication, withdrawn due to adverse effects or proved to be less efficacious. As a matter of fact, most of the drug repositioning emerged as a result of beneficial side effects (by serendipity); however, current efforts to attain repurposing are accomplished in a more systematic way (Naveja et al. 2016). Nowadays, the problem of antimicrobial drug resistances poses a growing threat to global public health and demands newer or repositioned drugs. With regard to utilizing already FDA-approved drugs for another indication, the entities can be used for treating the new indication without any further structural modification of the compound at hand (though dosing and formulation could be modified) (Savoia 2016; Klug et al. 2016). The case of Ebola virus outbreak in West Africa that reached to a scale not ever seen in history was the greatest public health emergency. Antibody-based therapy was proved effective in a macaque model and had been used to treat few patients; however, the supply of the drug was quite limited. Therefore, drug repurposing was the best option to come up with an old drug with new indication to speed up the discovery and development of anti-Ebola virus drugs for the treatment of patients with Ebola virus infection. As a result, initial drug repurposing screen subsequently provided 53 approved drugs with Ebola virus-like particle entry-blocking activity including the macrolide antibiotics azithromycin and clarithromycin, which block bacterial protein synthesis (Kouznetsova et al. 2014). Finally, six antibiotics which inhibit Ebola virus infection (azithromycin, erythromycin, spiramycin, dirithromycin, maduramicin, clarithromycin) were selected for anti-Ebola activity out of 3828 FDA-approved drugs (Veljkovic et al. 2015). There was no herbal therapy for Zika virus infection; however recently, two antiviral agents have been approved by FDA for Zika virus infection (Cheng et al. 2016). It is important to design or develop a therapeutic approach to overcome Zika virus infection with a special focus on drugs

targeting the virus helicase protein, nucleosides, inhibitors of NS3 protein, small molecules, methyltransferase inhibitor and repurposed drugs. Repurposed drugs such as chloroquine, azithromycin and niclosamide are used for the treatment of Zika virus infection (Munjal et al. 2017). New studies revealed that Alzheimer's drugs may moderate Zika virus-mediated neuronal damage. So, Alzheimer's disease drugs which overstimulate N-methyl-d-aspartate receptors (NMDARs) lead to damage neuronal death interlinked with Zika virus infection. Therefore, blocking of NMDAR channels with memantine and/or other antagonists helps to lessen the neuronal damage associated with Zika virus infection, which act as a pre-approved drug from the Food and Drug Authority (FDA) which need more clinical trials (Sirohi and Kuhn 2017).

Modification of specific or non-specific immune responses is a promising intervention for ongoing viral infections. The most suitable for immunotherapy are chronic viral infections (Hegde et al. 2009). The first example is monoclonal antibodies, which are specific for one to one antigen or one epitope. In fibroblasts and neuroblastoma cells, monoclonal antibodies specific for nucleoprotein and non-structural protein of the nucleocapsid have been shown to inhibit rabies virus, in a dose-dependent way, by impairing transcription of the genome or neutralizing newly translated proteins (Lafon and Lafage 1987). In addition, another study found that monospecific antibody against rabies virus nucleoprotein recognizes lyssavirus-specific antigen (Inoue et al. 2003). Monospecific antibodies have shown to be effective against non-capsid proteins of poliovirus (Pasamontes et al. 1986) and various livestock diseases as rotaviral diarrhoea, bluetongue, classical swine fever, Hendra and Nipah viral infections (Deb et al. 2013). Neutralization by antibody can be mediated by different mechanisms such as destabilization of the virion structure, aggregation of virions, inhibition of virion attachment to target cells, inhibition of the virion lipid membrane fusion with the membrane of the host cell, inhibition of the entry of the genome of non-enveloped viruses into the cell cytoplasm and inhibition of a function of the virion core through a signal transduced by an antibody (Reading and Dimmock 2007). Another therapeutic strategy for infectious viral diseases are recombinant antibodies, which, unlike monoclonal antibodies, do not need hybridomas and animals in the production process, but only synthetic antibody coding genes, and are delivered in high reproducibility, specificity and scalability (Echko and Dozier 2010). Examples include avian antibody against VP2 of infectious bursal disease virus protecting against viral infection in chicken (Zhang et al. 2017), porcine circovirus type 2 (Yang et al. 2014), the E2 protein of classical swine fever virus (Chen et al. 2018) and capsid protein of bovine immunodeficiency virus (Bhatia et al. 2010).

Antiviral drugs have been tested for various viral diseases of animals. Antiviral therapy has been developed against a number of RNA viral infections in livestock. First among them, against foot-and-mouth disease (FMD), involves vaccine that contains an inactivated whole-virus antigen. However, since vaccinated animals cannot be differentiated from the infected ones, the vaccine is not useful in eliminating FMD outbreaks from previously disease-free countries. Hence, interferons (IFNs) have emerged as another treatment agent, including IFN-α, IFN-β and

IFN-γ, which are used both individually and synergistically. IFN-γ has been described to have several targets that possess antiviral properties, such as indoleamine 2,3-dioxygenase and inducible nitric oxide synthase (Moraes et al. 2007). One of the most widespread diseases in domestic livestock is caused by another RNA viral infection, bluetongue virus (BTV). An aminothiophenecarboxylic acid derivative named compound 003 (C003) and its derivative compound 052 (C052) have been identified as virostatic molecules against BTV. They exert their effect by inhibiting BTV-induced apoptosis via inhibition of caspase-3/caspase-7 activation and inhibition of host autophagy activation (Gu et al. 2012). Furthermore, feline herpes virus type 1 (FHV-1) is a common cause of various diseases in cats, such as ocular surface disease, respiratory disease, dermatitis and potentially intraocular disease. A number of antiviral agents have been described against the virus, but the most effective antiviral therapies are the ones that target viral proteins involved in DNA synthesis, many of which have been used against closely related human herpes simplex virus type 1. For example, nucleoside and nucleotide analogues have been reported for topical administration, such as vidarabine that affects DNA polymerase and subsequently disrupts DNA synthesis, trifluridine which acts as a fluorinated nucleoside analogue of thymidine and cidofovir which is a cytosine analogue acting on two host-mediated phosphorylation steps (Thomasy and Maggs 2016). Purine analogues and their oral prodrugs have also been described as well as other antiviral drugs, such as foscarnet that inhibits pyrophosphate binding site on viral DNA polymerases, while numerous novel compounds have been investigated against FHV-1 including siRNAs which target the FHV-1 glycoprotein D (gD) alone or jointly with DNA polymerase genes (Wilkes and Kania 2010). To conclude with, equine herpesvirus type 1 (EHV-1) infection causes outbreak of respiratory and various neurological diseases in horses, against which acyclovir and valacyclovir are the most common drugs, but also IFN targeting IFNGR complex as a key mediator of virus-specific cellular immunity (Poelaert et al. 2018).

Feline immunodeficiency virus (FIV) is a complex lentivirus causing immunodeficiency disease in cats, manifested as the body's inability to develop normal immune response. As a retrovirus, it inserts copies of its genetic material into the DNA of a host cell, where it can replicate. The most commonly used antiretroviral drugs are reverse transcriptase inhibitors (RTIs), in particular the ones acting as nucleoside analogues, which are similar in structure to intrinsic nucleosides and can therefore block enzymatic activity by binding to the active centre of the enzyme (Hartmann et al. 2015). The first among them, zidovudine (AZT), has been reported to improve the immunologic and clinical status of FIV-infected cats, increase quality of life as well as prolong life expectancy. It has been shown to increase the CD4/CD8 ratio in naturally FIV-infected cats and acts by inhibiting RT but also cellular polymerases, which can lead to bone marrow suppression (Hartmann 1998). Another drug acting as RTI is stavudine that has been shown to be active against FIV in vitro, however with many resistant strains arisen. Similarly, didanosine and lamivudine have shown potency against FIV in in vitro conditions (Schwartz et al. 2014). Additionally, a combination of zidovudine and lamivudine has been investigated, resulting in synergistic anti-FIV effects in cell cultures. Also, a high-dose

zidovudine/lamivudine combination was shown to protect from infection when treatment was initiated before virus inoculation (Arai et al. 2002). Moreover, all of the above-mentioned antiviral agents are also effective against HIV infection.

Interferons (IFNs) are a multigene family of inducible cytokines that possess antiviral activity. The IFN system comprises the cells synthesizing IFN in response to an external stimulus, such as viral infection, and cells that respond to IFN by establishing the antiviral state. They represent an early host defence, the one that occurs prior to the immune response onset. IFNs are classified as IFN-α and IFN-β, which are produced by the cell in response to virus infection, and IFN-γ, synthetized upon antigen or mitogen stimulation (Samuel 2001). Their activity has been reported against a number of feline viruses, including feline calicivirus (FCV), where they act by stimulating downstream genes such as 2′-5′oligoadenylate-dependent ribonuclease L (RNase L), which degrades single-stranded viral RNAs. Also, feline IRF-1, shown to be reduced upon FCV infection, has been reported to positively regulate IFN signalling by triggering the production of endogenous IFN and the expression of downstream targeted genes (Liu et al. 2018). As mentioned before, another feline virus reported for IFN therapeutic solutions is FIV. The best known among them, recombinant RFeIFN-ω, is the first interferon compound that has been licensed for use in veterinary medicine, shown to significantly increase levels of acute phase proteins (APPs) (Doménech et al. 2011). RFeIFN-ω has also been reported for anti-inflammatory properties, exerted via interleukin-6 (IL-6) (Leal et al. 2015). Recombinant human interferon alpha-2b (rHuIFN-alpha2b) and recombinant feline interferon omega (RFeIFN-omega) have also exhibited an antiviral effect against feline herpesvirus (FHV)-1 in in vitro settings, as evidenced by significant reduction in plaque size (Siebeck et al. 2006). Interferons also showed therapeutic potential against feline leukaemia virus (FeLV), with recombinant feline interferon RFeIFN-omega, resulting in improvement of clinical signs and survival of infected cats (de Mari et al. 2004).

Idoxuridine and trifluridine are structurally similar thymidine analogues that inhibit synthesis of DNA. They have been applied in the treatment of feline herpesvirus-1 (FHV-1), significantly reducing the number of viral plaques in vitro (Nasisse et al. 1989). Idoxuridine has also exhibited therapeutic potential against equine herpesvirus type 2 (EHV-2) by alleviating the ocular symptoms caused by the infection (Collinson et al. 1994). It has also been reported that idoxuridine in the concentration of 0.1% and 0.3% trifluridine can limit the viral replication but do not kill the virus (Plummer et al. 2014).

Antiviral drugs and vaccines are the most powerful tools to combat viral diseases. However, they mostly selectively target only a single virus, known as a “one drug–one bug” principle. On the contrary, broad-spectrum antivirals (BSAs) cover multiple viruses and genotypes, therefore reducing the likelihood of resistance development. They can, hence, reduce the complexity of the treatment, ensuring management of new or drug-resistant viral strains, first-line treatment or prophylaxis of acute infections, as well as co-infections (Zhu et al. 2015). Against some viruses, such as hepatitis C, a direct-acting antiviral agents (DAAs) have been developed in the past few years. They act on NS3/4A protease inhibitors, NS5A

inhibitors or NS5B inhibitors and ensure efficient, tolerable, safe and interferon-free oral therapies (Das and Pandya 2018). Furthermore, further development of antiviral agents will not only focus on viral factors as the potential targets for inhibition but also on the host factors as well, such as cellular receptors, adhesion molecules, cyclophilins and microRNAs. Therefore, an effort will be put on the combination of viral and host inhibitors, eventually leading to interferon-free therapies for consistent clearing of infection (Bryan-Marrugo et al. 2015).

Perspectives for use of antiviral drugs in livestock animals are envisaged as the mass treatment for the control of the disease (on a large scale), whereas treatment in companion animals favours an individual approach. The main prerequisite for successful veterinary antiviral chemotherapy is a better understanding of the viral infection pathogenesis as well as development of sophisticated means for drug delivery. These will mainly focus on targeted approaches that aim specific molecular targets with a narrow niche, allowing for better specificity and less side effects of antiviral agents. Advances in the field of molecular biology, in particular computational approaches, would contribute to development of a new generation of antiviral therapy, which would be of importance in the control of various kinds of animal diseases.

22.15 Conclusions

The use of animal models for viruses of human and veterinary importance is still abundantly used to develop therapeutic agents. However, the current interest of these various viruses leads to multiple drug resistance due to the use of higher-dosage therapies. The approaches are different for companion animals as a single method is preferred, while for large-scale livestock, mass treatment therapy is used; that is why antiviral drugs and other natural as well as herbal products are characterized through a novel and optimistic approach. Still it is worthy to notice that these therapies lead to multiple drug resistance which should be overcome in the future.

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