Antiviral Nucleosides Synthesis

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Dr. Danveer Singh Yadav

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PREFATORY NOTE

Virus is a latin word which means poison. Viruses are submicroscopic pathogens which grow, flourish and propagate only in living cells. These and are the connecting links between the living and non-living. They can be kept as nonliving particles but as they come in contact with a living cell they start their reproduction, i.e. they are living. Viruses are strange parasites in the sense that they can propagate and grow only in living organisms and not in a lifeless culture or cell free media; they have the power of replication when present in right environment. It is not to be overemphasised that viruses had been with us and are with us all the time. Sometimes they are harmful and some times they are not. Keeping Louis Pasteur's view in mind that infectious diseases are caused by microorganisms, the Russian botanist Iva- novski (1892) gave the evidence of virus[1]. In 1886 Mayer demonstrated that when juice extracted from tobacco plant infected with mosaic disease was injected into healthy plant, it showed mosaic disease. Ivanovski then confirmed the above obser-vation and concluded that the agent was smaller than any bacterium. Bacteriophages (viruses found in bacteria) was discovered by 'd' Herelle (1917), a French scientist. Schelksinger (1933) showed that viruses consist of only proteins and nucleic acids. In 1935 tobacco mosaic virus was crystallized, and they retained their infectivity when injected into healthy plants.

Viruses are smaller than bacteria and most of the animal as well as plant viruses are invisible under the light

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microscope. The size of viruses may vary from 20 to 300 nm. Some viruses may also be larger than bacteria. The virus of *lym- phogranuloma venereum* has diameter of 300-400 mu Generally, viruses are slightly larger than larger protein and nucleic acid molecules. The mouth diseasevirus is smaller than largest protein molecules. Since viruses are invisible under the light microscope, their size is determined by electron microscope, ultracentrifugation and by filtration through colloidon membranes. Generally, viruses are of spherical, helical or complex shape.

Chemically, viruses are nucleoproteins containing either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) surrounded by a protecive protein sheath . It has been reported that some of the animal, bacterial and plant viruses also contain lipids and carbohydrates.

The composition varies qualitatively as well as quantitatively from virus to virus although exceptions are there. Bacteriophages and animal viruses are DNA viruses and plant viruses are RNA viruses. Exceptions are found in both the cases, e.g. influenza virus is a RNA containing virus while cauliflower mosaic virus is a DNA containg virus. Depending on the single or double stranded, straight chain or cyclic structures of nucleic acids, there could be eight types of viruses :

(i) Double stranded DNA, e.g. herpes siplex

(ii) Single stranded DNA, e.g. coliphage virus.

(iii) Double stranded RNA, e.g. wound tumour virus.

(iv) Single stranded RNA, e.g. tobacco mosaic virus.

(v) Double stranded cyclic DNA, e.g. Polyoma virus.

(vi) Single stranded cyclic DNA, e.g. coliphage f× 174 virus.

(vii) Double stranded cyclic RNA.

(viii) Single stranded cyclic RNA, e.g. potato spindle tuber virus.

Protein forms the outer sheath which gives the virus particle their charac-teristic shape. In certain complex viruses

some internal protein entities are also found,and a few of them have been reported to be enzymic, e.g. phage lysozyme and influenzal neuraminidase are associated with bocteriophages and influenza virus, respectively.

In certain cases, a viral nucleic acid may remain naked in a host cell. Carbohydrates, viz. deoxyribose and ribose are always associated with viral nucleic acids. Besides these, nonnucleic acid carbohydrate moieties, viz. glucose and gentiobiose are also found in the form of glycoproteins or glycolipids in animal and plant viruses.

(Viruses are responsible for various dreadful diseases of both animals and plants.) The animal diseases caused by viruses were known from ancient time. Previously, some of these diseases were linked to unnatural and supernatural causes. Pujas and offerings were performed to please the gods and goddesses thought to be responsible for the diseases. For example, goddess Sitala was considered responsible for small pox and worshipped by millions of our countrymen.

(Viral diseases may take the form of epidemics.) Sixty million people died of small pox alone during the eighteenth century. This epidemic also occured in Bihar in 1973-74 which is still fresh in our minds. Similarly, another viral disease influenza has been claiming lives in millions. Yellow fever, a tropical disease, used to cause deaths in thousands in tropical countries of Africa and central America.

In the present decade, the major threat to the human civilization is from AIDS virus in which the immune system collapses. This virus is called human immune defficiency virus (HIV). In the years to come, it may take the form of epidemic. Certain viruses are also known to cause cancer, e.g. herpes simplex virus type - 2 causes corcinoma of the uterus cervix in women. Other common diseases caused by viral infections in human are; poliomylitis, encephalitis, measles, infectious hepatitis, viral bronchitis, hydrophobia and common cold.

Not only to animals and humans but also viruses are equally harmful to plants. More than three hundred viral

diseases of plants have been recorded,. Some of the major plant diseases are tobacco mosaic disease, tomato leaf curl, potato leaf roll, cucumber mosaic, pumpkin mosaic, tulip break, and papaya mosaic. Since our economy is mainly dependent on the agriculture, the viruses affect the economy considerably by causing a great loss of crop yields, (viruses also affect the industry, for expample, the production of viral based vaccine is a major attempt related to medicine. This includes cultivation of specific viral strains, pathogenic for a disease, under controlled conditions, and the desired immunogen is obtained. Haffkme Institute, Bombay and Bengal immunity centre in Calcutta are main institutions in India which produce vaccines on commercial scale. *Streptomyces* are used in bakeries and breweries. Similarly, *Azobacter* and *Clostridium*, the nitrogen fixing bacteria in rice fields, are destroyed by bacteriophages.

Cyanophages are harmful to blue green algae which fix the atmospheric nitrogen in rice fields. Bacteriophages and cyanophages also influence the sewage disposal based on activities of certain bacteria, e.g. *Micrococcus, Cytophages, Pseudomonas* and blue green algae *Plectonema.* Thus, all these are the direct or indirect hazards to human civilization.

The viral infection takes place with complete virus after that in some cases the whole virus passes to the host cell as in case of totabacco mosaic virus (TMV), while in others only the genetic metariaÏi.e. nucleic acid of virus is passed to the host cell, e.g. in case of bacteriophase. This viral genetic matarial replicates and starts synthesising the nucleic acids and proteins. The site is ribosome of the host cell itself It is predicted that host cell genetic metarial also supports the formation of viralproteins and nucleic acids. How they turn in favour of viral physiology is still unclear. Thus, the host cell physiology collapses and the disease becomes apparent. Symp-toms of plant diseases maybe internal symptoms or external, e.g. chlorosis, mosaics, vein clearing, blue green colour of leaves, curling of leaves outwards or inwards, retarded growth or stunting, tumours etc. are external

symptoms. Internal inclusion bodies are formed. These may be crystalline or amorphous (X-bodies).

In case of animals, the common symptoms are fever, bodyache, chill as in case of influenza, external and internal necrotic lesions as in case of poxes, paralysis of limbs as in case of polimyelitis. Some viruses are also known to induce tumours.

The transmission of viral diseases may take place either through interme-diate organisms called vectors or can be transmitted without intervention of any vector. The nonmediated transmission may be air borne, through physical contact with diseased host, heriditary in nature. Most of the vectors are insects, sometimes anthropodes e.g. mites, nematodes and fungi also act as vectors. The relationship between vector and virus is such that vetor is an intermediatory host for the virus.[1] *Myzus persicae* belonging to order hemiptera of insects is vector for more than 50 viruses. Certain grasshoppers and bettles (coleoptera) also act as vector. The wheat streak virus is transmitted by mite species *Acoria tulipae heifer* (Anthropode). Nematode *Xiphenema americanum* transmits tobacco ring spot virus (TRS V). Fun-gus *Olpidium brassicae* transmits tobacco necrosis virus (TNV) through it zoospores.

Animal viruses are similarly transmitted by vectors mechanically or bio-logically, e.g. yellow fever virus involves mosquito, polio virus of mouse involves cockroaches. Transnission of virus causing yellow fever and enquine encephalitis involves biological association with insect vectors.

The viral deseases in plants as well as in animals can be checked by preventing mechanical contacts and eradicating the vector, e.g. insects can be killed by applying certain insecticides, like gammexane, DDT, etc. Another powerful method is by immunizing the host. In animals, immunization is easy due to the presence of immune system

but this is absent in plants, therefore, immunization is difficult in case of plants. However, in case of plants we can produce certain resistant varieties which have resistance for a particular strain of virus.

The lymph cells in human produce special type of protein entities called antibody to counteract foreign invasion. The virus particles here act as antigens. Antibodies can be produced by applying inactivated virus particles, which does not harm the host cell. Recently, it was indicated that neutralization of infective virus particles with antibodies checks the release of nucleic acids from virus particles. First case of immunization was successful vaccination against small pox by Edward J enner (1796) . He got Nobel prize for his work. A single antibody can neutralize one infecting viral particle. Antibody does not interfere with adsoption of virus particle to the cell surface.

To control the viral diseases prophylactic as well as therapeutic chemical agents were synthesised. Since viruses are dependent on host cell for their physiol-ogy, any adverse effect on viral physiology will affect the host cell physiology to the same extent. Rifamycins is the only group of antibiotics having antiviral activity. This antibiotic is capable of repressing RNA dependent RNA and DNA synthesis. The backbone of viral chemotherapy is the quantitative difference. By using chemical agents in controlled doses the viral nucleic acid metabolism could be selectively inhibited without inhibiting the host cell nucleic acid metabolism. Similarly, formation of capsid and adsorptions to the receptor site of host cell can be checked.

The antiviral compounds are mainly base analogues of pyrimidines and purines required for nucleic acid synthesis. These get incorporated in new DNA which is functionlly ineffective, therefore, progeny virus is noninfectious. Structures and names of some antiviral agents are given on the next pages. Other important antiviral agents used in

therapy are substituted benzimidazole and guanidine derivatives. These are effective against RNA virus. Similarly, isatin - betathiosemicarba- zone is effective against pox virus. This selectively inhibits protein synthesis, interfering with function of m-RNA. Amantadin and its derivatives are most suc-cessful antiviral agents. These are useful prophylactic agents against influenza virus.

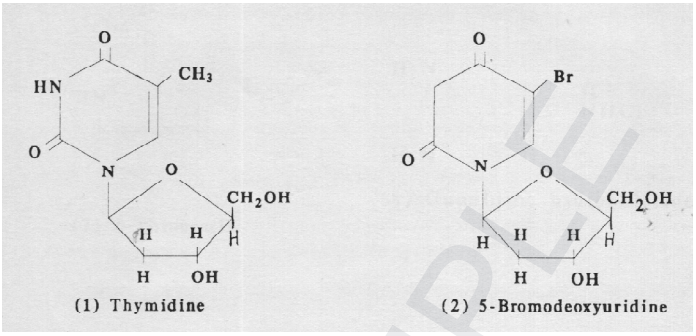
Some antiviral agents for plants chemotherapy are also available, e.g. solution of hydroquinone, urea, and sodium thiosulphate destroy X- virus of peach. Similarly, 6-azauracil, 2- thiouracil and 8- azaguanines are effective against tobacco mosaic and turnip yellow mosaic.

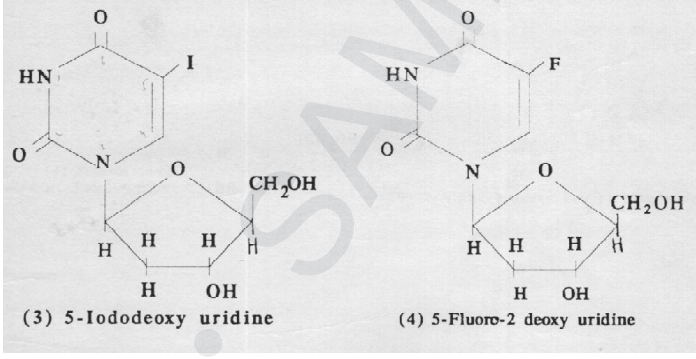
It is seen that compounds 2,3, and 4 are substitute for thymidine inhibits DNA synthesis and 8 and 7 are substitute for uridine, inhibits RNA polymerase and capsid formation respectivly, Similarly, Isatin- beta thiosemicarbazone 12 and 1- admantanamine II are substitute for uridine.

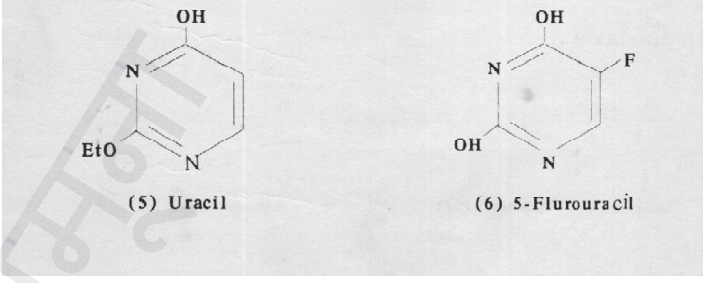
As abovementioned, most of the commercially available antiviral agents for both animals and plants are nucleosides. The nucleosides have two parts,viz. a heterocycle moiety and a sugar moiety. The antiviral activity of nucleosides is attributed to the presence of both of these moieties in a right combination.

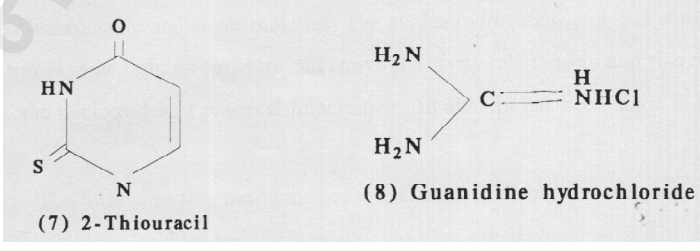
The up-to-date literature reveals that useful antiviral activity may be expected from novel nucleosides if the nucleosides are designed with a suitable heterocyclic system and the sugar moiety. In view of the above background and with the aim of further exploring the subject, it was considered worthwhile to undertake a systematic search for novel antiviral nucleosides designed with different combinations of heterocyclic and sugar moieties. The evaluation of their antiviral activity might throw some light on structure and antiviral activity relationship and also may yield some nucleosides of practical importance. An attempt has been made in this direction.

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(2) 5-Bromodeoxyuridine


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(3) 5-Iododeoxy uridine
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(4) 5-Fluoro-2 deoxy uridine


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(5) Uracil
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(6) 5-Flurouracil


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(7) 2-Thiouracil
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C
H
NHCl
H2N
(8) Guanidine hydrochloride

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