Virucidal agents are chemical substances that attack and inactivate viral particles outside the cell (virions). In general this is accomplished by damaging their protein shells (capsid) or the substance penetrates the core itself, where it destroys the genetic material. Damage to the virion structure is also possible. These agents are used not only for traditional surface disinfection or sterilization of blood, blood products, and other medicinal products as well as in antiviral chemotherapy. They have also been used in recent times for inactivation of viruses in foodstuffs, detergents or cosmetics. Below is given an overview of the data currently available on the performance of these substances when used for the latter applications (cleaning and cosmetics). These include:

- hydrogen peroxide, hypochlorites, cupric and ferric ions, per-acids
- ethanol, parachlorometaxylenol in a sodium C14-16 olefin sulfonate, glutaraldehyde, quaternary ammonium salts, chlorhexidine and chlorhexidine gluconate, curdline sulphate, glycerol, lipids, azodicarbonamide, ciclohexalone sodium, dichlorisocyanuric acid (sodium salt), benzalkonium salts, disulfate benzoamides and benzisothiazolones, congo red, ascorbic acid, nonoxynol-9, para-aminobenzoic acid, bis(monosuccinamide) derivative of p,p'-bis(2-aminoethyl) diphenyl-C60) (fullerene).
- merocyanine, benzoporphyrin derivative monoacid ring A, rose bengal, hypericin, hypocrellin A, anthraquinones extracted from plants, sulfonated anthraquinones and other anthraquinone derivatives
- gramicidine, gossypol, garlic (Allium sativum) extract and its components: ajoene, diallyl thiosulfinate (allicin), allyl methyl thiosulfinate, methyl allyl thiosulfinate, extracts of ledium, motherworth, celandine, black currant, coaberry and bilberry, extract of Cordia salicifolia, steam distillate from Houttuynia cordata (Saururaceae) and its component, 5,6,7-trimethoxyflavone from Calicarpa japonica, isoscullarein (5,7,8,4'-tetrahydroxyflavone) from Scutellaria baicalensis and isoscutellarein-8-methylether, alkaloïds and phytoesteryl ester compounds.

Zusammenfassung

Virusinaktivierende Stoffe sind chemische Substanzen, die Viruspartikel angreifen und inaktivieren, die sich außerhalb der Zelle befinden (Virion). Im Allgemeinen geschieht dies, indem deren Proteinhülle (Capsid) beschädigt wird oder die Substanz in den Kern selbst eindringt und dort das Erbgut zerstört. Möglich ist auch die Beschädigung der Virion-Struktur. Diese Agens werden nicht nur in der klassischen Flächendesinfektion oder der Sterilisation von Blut, Blutprodukten und anderen Arzneimitteln bzw. in der antiviralen Chemotherapie eingesetzt, sondern neuerdings auch zur Inaktivierung von Viren in Lebens- und Reinigungsmittel sowie Kosmetika. Es wird eine Zusammenstellung über die aktuell bekannte Leistungsfähigkeit dieser Wirkstoffe im letzten Anwendungs bereich (Reinigung und Kosmetik) gegeben.
Introduction

Virucidal agents represent chemical substances (individual compounds or compositions) attacking and inactivating (decreasing the infectivity of) the extracellular viral particles (virions). Principally, virucidals damage the virion protein capsid or supercapsidal membrane, or penetrating into the virion destroy the viral genome. The viral particle integrity could also be affected.

Four major application fields of the virucidal agents could be distinguished, namely:

1. Disinfection of the environment - historically this is the oldest and still widely developing field.
2. Sterilization of biological products for parenteral administration: blood, blood products, medicinals.
3. Antiviral chemotherapy - some antiviral agents could exert virucidal mode of action as a specific or secondary effect.
4. Elimination of viruses from food, sanitary products and cosmetics. This is the newest and most prospective field of application.

The following literary update involves substances manifesting distinct virucidal properties making them potentially suitable to be used in sanitation and cosmetics. Some of them have been already registered as disinfectants or blood products sterilyzing agents.

Inorganic compound

Peroxide

Hydrogen peroxide (known as a disinfectant) in solution (3%-6%) showed a very low virucidal effect towards enteroviral virions (1 min treatment in the surface test vs. poliovirus 1 dried suspension) or lack of effect (1 min in the suspension test) [1].

Hypochlorites

High concentrations (9200 ppm avCl2) were effective (a >4 lg reduction) against a dried enterovirus (poliovirus 1) suspension (in the surface test) in 1 min. Lower hypochlorite concentrations (1000 ppm avCl2) were less effective [1].

Cupric and ferric ions

These metal ions were able to inactivate a comparatively wide spectrum of enveloped or nonenveloped, ss- or ds RNA or DNA viruses, e.g. Junin (arenavirus), herpes simplex viruses 1 and 2, and different phages (X174, T7, 6). The virucidal effect of these metals was enhanced by the addition of peroxide, particularly for copper (II). The combinations mentioned above should be able to inactivate most, if not all, viruses that have been found contaminating medical devices [2].

Per-acids

Per-acid based disinfectants are known as powerful viricides. Some commercial preparatives (e.g. “Peral-S” disinfectant) revealed a strong virucidal activity on entero-virus (Coxsackie B6 virus) and herpesvirus (herpes simplex virus 1) at 0.1% concentration within 30 seconds only. The so-called “floating technique” was applied in this study [3].

Organic compounds

Ethanol

At 70% this compound showed variable results in a virucidal testing (surface test) vs. the enterovirus polio 1, while in the suspension test was ineffective in 1 min [1].

Parachlorometaxylenol in a sodium C14-16 olefin sulfonate

At 0.5% this composition proposed as soap (for a health care personnel hand wash) demonstrated a strong virucidal effect against HIV1 in the presence of 50% whole human blood within 30-60 sec. More than 99.9% of the virus was inactivated at 1:5 - 1:30 dilutions [4].

Glutaraldehyde

At 2% this compound was effective in the surface test on poliovirus 1 (> 4 lg reduction) for 1 min [5]. A 2% alkaline glutaraldehyde was efficient as a virucidal and bactericidal agent against a mixture of some picornaviruses (hepatitis A and poliovirus 1) and some bacteria (Pseudomonas aeruginosa, Mycobacterium bovis and Mycobacterium gordonae) in the so called carrier test (with a contact time 10 min at 20°C). The criterion of efficacy was a minimum of 3-log reduction in the infectivity titers of the organismes tested. In this case the use of the compound was endoscopes disinfection via baths [6].

Quaternary ammonium salts

A newer generation of quaternary ammonium compounds showed a distinct virucidal effect against calici-, parvo- and herpesviruses (causative agents of diseases in domestic cats and dogs) for à 10-min contact at room temperature [7].
Chlorhexidine and chlorhexidine gluconate

Chlorhexidine could be considered as efficient vaginal virucidal preventing heterosexual transmission of HIV [8]. The gluconate derivative at 0.12% concentration (proposed for a mouthrinse preparative) was effective on a unusually wide spectrum of viruses: influenza A, parainfluenza, HSV, CMV and HBV. The poliovirus was unsensitive. The contact time was 30 sec [9]. The probable mode of action is an interaction with the virion envelope, and the differences in the virucidal effects are based on differences in the physical/chemical structures of the virus envelopes [9].

Cicloxolone sodium

This compound manifested a wide-spectrum virucidal effect: towards HSV-1, HSV-2, VSV, adenoviruses (type 5). A relocation of assembled virus is presumed. Besides, a very well pronounced inhibitory effect on the replication of different virus families (picorna-, reo-, toga-, bunya- and adenoviruses) was established [14].

Dichlorisocyanuric acid (sodium salt)

The compound revealed a marked virucidal activity against ectromelia virus (poxvirus family). It is proposed for use as a water disinfectant [15].

Curdline sulfate

This newly synthesized sulfated polysaccharide preventing the binding of HIV to the surface of H9 cells exhibited a weak virucidal activity [10].

Benzalkonium salts

This group of positively charged surface active alkylamine biocides interacts with guanine nucleotide triphosphate-binding proteins. Benzalkonium salts have antiproliferative effects on a variety of cells, affect cytokine gene expression, and are also effective virucidal, bactericidal and fungicidal agents. Virucidal activity was found against HIV, papillomaviruses and herpesviruses [16].

Glycerol

This substance known as a viral preservation medium in tissue samples at a 50% concentration for a short period of time, applied at higher concentrations showed a strong virucidal activity at different temperatures (4, 20 and 37°C) against HIV, HSV1 and polioviruses. Both a dehydrating action and an influence on the enzymatic processes of nucleic acid breakdown are discussed as the possible base of the glycerol action. Otherwise, glycerol is known to dehydrate the skin, the extracted water being replaced by glycerol, preserving the original structure [11].

Disulfate benzamides and benzisothiazolones

A group of 4 derivatives possesses anti-HIV virucidal activity based on an ejection of zinc from the virus nucleocapside protein [17].

Congo red

This membrane-binding dye inactivates HIV in the presence of magnesium dichloride (Mg²⁺ ions) only. This effect was found to be reversible as validated by washing of the cells by Hanks’ solution + MgCl₂ following capture of the virions from cell-free HIV-Congo red inactivation mixture [18].

Ascorbic acid

Vitamine C demonstrated a virucidal effect on HIV in the presence of Mg⁺⁺ ions. Its virucidal properties are closed to those of Congo red [18].

Lipids

Purified lipids can inactivate enveloped viruses, bacteria, fungi, and protozoa. This activity is attributed to certain monoglycerides and fatty acids that are released from triglycerides by lipolytic activity. Medium chain length antiviral lipids can be added to human blood products that contain HIV-1 and HIV-2 and reduce the cell-free virus concentration by as much as 11 lg TCID₅₀/ml. Antimicrobial lipids can disrupt cell membranes and subsequently lyse leukocytes which potentially carry virus [12]. Preliminary studies indicate that lipids decrease sperm motility and viability suggesting that lipids may potentially be used as combination spermicidal and virucidal agents [12].

Nonoxynol-9

This a virucidal and spermicidal agent used for vaginal treatment preventing heterosexual transmission of HIV or for impregnation of surgical gloves serving as a barrier for HIV infection [8], [19], [20].

Azodicarbonamide

This compound is a nuclucapsid inhibitor efficient against HIV-1 and other retroviruses, and its virucidal effect is based on the prevention of reverse transcription initiation and a block of infectious virion formation from cells [13].
Para-aminobenzoic acid

This compound showed a marked anti-herpesvirus (HSV-1) activity both in vitro and in vivo, and virucidal mode of action was presumed [21], [22].

Bis(monosuccinamide) derivative of p,p'-bis(2-aminoethyl) diphenyl-C60 (Fullerene)

This substance showed activity against HIV-1 and HIV-2. Its virucidal properties were confirmed by the contact (virus-inactivating) test. In cell-free system fullerene manifested comparable activity against HIV-1 reverse transcriptase and DNA polymerase (alpha), and a selective activity towards HIV-1 protease [23].

Photosensitizing virucidal agents

Merocyanine

This pyrimidinone derivative, a lipophilic dye, is a photosensitizing virucidal agent efficient vs. lipid-containing, enveloped, viruses, e.g. HSV. Its activity was proved initially on bacteriophages as surrogate for animal viruses [5].

Benzoporphyrin derivative monoacid ring A

This compound destroyed enveloped viruses (HIV) in blood and blood products when activated by light. Its eliminates the virus but did not damage blood cells or blood components [24].

Rose bengal

Virucidal spectrum of this compound envolves various groups of enveloped viruses: orthomyxo- (influenza A), paramyxo (Sendai), rhabdo- (VSV) and retroviruses (HIV, Friend leukemia virus) [25], [26], [27]. HIV and VSV were photodynamically inactivated by this dye at nanomolar concentrations [25]. The non-enveloped viruses are unsusceptible. The compound inactivated influenza virus upon exposure to light. It was established that the virucidal activity of photodynamically agents against enveloped viruses may be generally due to inactivation of their fusion protein(s). Concentrations required for inactivation were found to depend upon the ratio of rose bengal to virus, rather than on nominal aqueous concentration. The HA2 portion of influenza fusion protein HA underwent two different apparently mutually exclusive modifications upon illumination with rose bengal. Inactivation of the viral fusion was inhibited by oxygen removal or addition of azide or beta-carotene, and was enhanced by D2O, consistent with partial involvement of singlet oxygen. A direct interaction between the viral fusion protein and the photoactivated dye is also possible [26].

Hypericin

This natural polycyclic anthrone, first isolated from the plant St. Johnswort manifested is a strong photosensitizing lipophilic virucidal agent. Its effectivity was found upon influenza A virus, Sendai virus, VSV, HIV and other retroviruses (murine Friend leukemia virus, radiation leukemia virus and Moloney mouse leukemia virus, equine infectious anemia virus), HSV-1, HSV-2 and vaccinia virus [25], [27], [28], [29], [30], [31], [32]. The compound photodynamic virucidal efficiency vs. HIV and VSV was found at nanomolar coconcentration [25]. Hyperacini did not showed selective antiviral activity against HSV, influenza A, adeno- or poliovirus. When virus was incubated hypericin before infecting cells, the drug was virucidal to all enveloped viruses tested (influenza A, Moloney mouse leukemia virus, HSV). The compound was not virucidal to the none-enveloped viruses (polio, human rhinovirus, adeno) tested. Evidently, the mechanism of viral inactivation for hypericin is dependent upon the presence of a viral lipid envelope [28]. The chemiluminescent oxidation of luciferin by a plant luciferase was found to generate sufficiently intense and long-lived emission to induce virucidal activity of hypericin [29]. Hypericin bind cellmembranes (and by inference, virus membranes) and crosslinks virus capsid proteins. Its anti-retrovirus action results in a loss of infectivity and an inability to retrieve the reverse transcriptase enzymatic activity from the virion [30]. Hypericin is convienient for use as virucidal (vs. HIV) treatment of blood products [30]. Addition of small amounts of Tween-80 to solutions containing hypericin enhanced by up to 2.6 lg hypericin’s virucidal activity [32].

Hypocrellin A

This compound displays photoinduced virucidal activity, in particular against HIV. Hypocrellin A like hypericin exectutes an excited-state intramolecular proton transfer, and defferes from hypericin in two important ways: a. hypocrellin A absolutely requires oxygen for its virucidal activity; b. hypocrellin A does not acidify its surrounding medium in the presence of light [30].

Anthraquinones extracted from plants

Several virucidal compounds from this class were isolated from different plants (Rheum officinale, Aloe barbadensis, Rhamnus frangula, Rhamnus purshuana, Cassia angustifolia), namely emodin, aloe-emodin, emodin anthonvre and emodin bIanthe. Hypericin is also a member of this class. Their virucidal spectrum envolves a large scope of enveloped viruses: influenza, parainfluenza, VSV, herpesviruses HSV-1, HSV-2, VZV and PsRV [32], [33]. The compound effective concentrations were less than 1 mcg/ml in the so-called contact (direct pre-infection incubation) test. The activity of these substances
were lower than that of hypericin. By their virucidal effects the compounds could be arranged as follows: emodin bianthrone > emodin anthrone > emodin [32]. Aloe-emodin inactivated all of the viruses mentioned above; adenovirus and rhinovirus were insensitive [33].

**Sulfonated anthraquinones and other anthraquinone derivatives**

Anthraquinone derivatives acid blue 40 and 129, acid black 48, alizarin violet R and reactive blue 2 manifested a marked virucidal activity upon human CMV strains [34].

**Natural products**

**Gramicidine**

This polypeptide antibiotic derived from Bacillus brevis is a weak anti-HIV virucidal (thousand-fold less active than nonoxyl-9 and gossypol [20].

**Gossypol**

This substance, a polyphenolic aldehyde extracted from cotton seed, demonstrated several biological effects: a pronounced interferon-inducing activity, a contraceptive (spermicide) and an anti-HIV virucidal effects [20], [35]. The latter was proved in cell-free reverse transcriptase system.

**Garlic (Allium sativum) extract and its components: ajoene, diallyl thiosulfinate (allicin), allyl methyl thioulnfinate, methyl allyl thiosulfinate**

Garlic has been shown to have antiviral activity. In the contact test the fresh garlic extract and several garlic associated compounds as mentioned above demonstrated a strong virucidal activity against wide spectrum of viruses - enveloped (parainfluenza virus type 3, VSV, HSV-1, HSV-2), non-enveloped (human rhinovirus type 2) and vaccinia virus as well. The order for virucidal activity of the garlic extract compounds was: ajoene > allicin > allyl methyl thiosulfinate > methyl allyl thiosulfinate. Ajoene was found in oil-macerates of garlic but not in fresh garlic extracts. No activity was found for the garlic polar fraction, alliin, deoxyalliin, diallyl disulfate, and diallyl trisulfate. Fresh garlic extract, in which thiosulfinates appeared to be the active components, was virucidal to each virus mentioned above. Experimental data demonstrated that virucidal activity and cytotoxicity may have depended upon the viral envelope and cell membrane, respectively [36].

**Extracts of ledium, motherworth, celandine, black currant, coaberry and billberry**

The aqueous extracts of these plants manifested a virucidal effect towards tick-born encephalitis virus and induced resistance in mice infected with this virus [37].

**Extract of Cordia salicifolia**

A partially purified extract of this plant has been shown to have a direct virucidal activity against HSV-1, to which could be attributed the inhibitory effect of this extract on viral replication [38].

**Steam distillate from Houttuynia cordata (Saururaceae) and its component**

The steam distillate prepared from fresh plants was found to have virucidal activity against several enveloped viruses: influenza A virus, HIV and HSV-1. Three major components of the distillate, methyl-n-nonyl ketone, lauryl aldehyde, and capryl aldehyde, also inactivated these viruses. The data obtained demonstrate that the essential oils provide virucidal activity against enveloped viruses by interfering with the function of the virus envelope [39].

**5,6,7-Trimethoxyflavone from Calicarpa japonica**

This naturally occurring flavone exhibited relatively high inhibitory effect on replication of poliovirus 1 and herpes-viruses HSV-1 and CMV. The anti-HSV-1 action is not due to the inhibition of virus adsorption, entry, and viral protein synthesis, but might involve, at least in part, a virucidal activity, which results in a suppression of viral binding to host cells at an early replication stage [40].

**Isoscullarein (5,7,8,4’-tetrahydroxyflavone) from Scutellaria baikalensis and isoscutellarein-8-methylether**

These substances isolated from the plant leaf demonstrated both an inhibitory effect on the influenza A virus neuraminidase and a potent virucidal activity against this virus in ovo and in vivo. The virus-inhibitory effect of flavone and methylether were identical, but the flavone’s virucidal activity was stronger [41].
Alkaloids and phytosteryl ester compounds

These substances (marigenol-concentrates comprising taxol and/or taxan esters as active principles) manifested an anti-tumor and antiviral/virucidal activity [42].

This was in general lines the virucidal agents’ spectrum before the appearance of the pioneer of a new generation rubs, Manorapid Synergy® [43], [44].

Abbreviations

Abbreviations used: CMV - cytomegalovirus; HA - hemaglutinine; HBV - hepatitis B virus; HIV - human immunodeficiency virus; HSV - herpes simplex virus; PsRV - pseudorabies (Aujesky’s disease) virus; TCID50 - 50% tissue culture infectious dose; VSV - vesicular stomatitis virus; VZV - varicella zoster virus.

Curriculum Vitae

Angel S. Galabov, Ph.D., D.Sc.

Figure 1

Professor of Virology, Head of Department of Virology, Institute of Microbiology, Bulgarian Academy of Sciences, Sofia. Angel S. Galabov reads medicine at the University in Sofia, where he takes his doctorate in 1962. He habilitates in 1968 at the Institute for Microbiology of the Bulgarian Academy of Science and afterwards moves - in the context of a scholarship - to the Louis Pasteur Institute in Paris to the winner of the Nobel Price, Andre Lwoff. Back in Sofia he manages from 1972 on the „Viral Inhibitors and Interferon Laboratory”, Department of Virology, Institute of Infectious and Parasitic Diseases, Medical Academy, Sofia and at the same time is Associate Professor of Virology, at the Department of Virology, Institute of Infectious and Parasitic Diseases, Medical Academy, Sofia. In between he moves to the National University of Moscow. Back in Sofia he is appointed Head of the Department of Virology, Institute of Microbiology, Bulgarian Academy of Sciences, Sofia. Professor Galabov is an internationally outstanding personality among the virologists: he has an extraordinary expertise in this demanding subject, almost 160 publications and 39 patents are proving it. His special interest is in the development of virus inactivating agents and therefore infection abatement. He researches the biological reactions of Interferon, interferon inducers, antioxidants, virucidal agents (disinfectants, sanitation agents), replication cycle of picorna, toga, flavi, orthomyxo-(influenza), paramyxo-, adeno- and herpes viruses, influenzavirus proteins, viruses – diabetes, viral role in the Balkan endemic nephropathy.

Prof. Galabov is a highly acknowledged member not only of nationally but also of internationally essential organizations, founder e.g. of the Balkan Society for Microbiology (BSM) or the first European International Symposia chain on Antiviral Substances.

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