Antiviral Activities of Zn\(^{2+}\) Ions for Viral Prevention, Replication, Capsid Protein in Intracellular Proliferation of Viruses

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ABSTRACT

In zinc homeostasis, zinc transporters ZIP and ZnT show tissue specificity and developmental and stimulus responsive expression patterns. The course of the life cycles of viral infections is governed by complex interactions between the virus and the host cellular system. Viruses depend on a host cell for their protein synthesis that the virus must first bind to the host cell, and then the virus enters in the cytoplasm which the genome is liberated from the protective capsid and, either in the nucleus or in the cytoplasm. The use of cellular zinc metalloproteases is effective for virus entry and coronavirus fusion. Molecular aspects of dengue virus genome uncoating and the fate of the capsid protein and RNA genome early during infection were investigated and found that capsid is degraded after viral internalization by the host ubiquitin-proteasome system. These results provide the first insights for antiviral intervention into dengue virus uncoating by Zn-binding degradation and enzyme inhibition of nucleocapsid, capsid protein, viral genome. AZPs inhibit virus DNA replication. Increasing the intracellular Zn\(^{2+}\) concentration with zinc-ionophores like pyrithione can efficiently impair the replication of a variety of RNA viruses, including poliovirus and influenza virus. ZAP is a host antiviral factor that specifically inhibit the replication of certain viruses, including HIV-1, Sindbis virus, and Ebola virus. ZAP specifically binds to the viral mRNA and recruits the cellular RNA degradation machinery to degrade the target RNA, while molecular mechanism by which ZAP inhibits target RNA expression and regulation of antiviral activity have been remained unclear. ROS as byproducts play an important role in cell signaling and regulate hormone action, growth factors, cytokines, transcription, apoptosis, iron transport, immunomodulation, and neuromodulation which...
many retroviruses, DNA and RNA viruses can cause cell death by generating oxidative stress in infected cells.

**Keywords:** Zinc finger, HIV, DNA/RNA virus, Replication, Capsid protein, RNA degradation, ROS


1. **INTRODUCTION**

Micronutrient homeostasis is a key factor in maintaining a healthy immune system. Trace element zinc is a critical cofactor for many proteins involved in cellular processes like differentiation, proliferation and apoptosis that zinc is a nutritionally fundamental trace element and is second most abundant trace metal in the human body after iron. Zinc’s significance as a structural component in many proteins and its participation in numerous cellular functions is now well established that such functions include cell proliferation and differentiation, RNA and DNA synthesis, as well as cell structures and cell membrane stabilization [1]. Zinc is involved in many metabolic and chronic diseases such as diabetes, cancer, neurodegenerative diseases, whereas there is also strong establishment between zinc deficiency and several infections such as malaria, human immunodeficiency virus (HIV), tuberculosis, measles, and pneumonia. In zinc homeostasis, zinc transporters ZIP (Zrt/Irt-like proteins) and ZnT (Zinc transporters) show tissue specificity and developmental and stimulus responsive expression patterns that on a cellular and subcellular level, they are also localized in specific compartments in which both transporter families respond to various stimuli such as zinc deficiency and excess by displaying specific changes in cellular localization and protein stability [1].

It will be prudent to revisit the physiological aspects of zinc metabolism before discussing zinc deficiency state. An average adult weighing 70kg has a body zinc content of 1.4～2.3 gm, the highest tissue concentration being in the prostate, seminal fluid, uveal tissue, and skin. While about half of the total body zinc is in the bones, the skin contains nearly 6% of total body zinc. As movement of zinc across various tissues is limited and there is no storage depot, the continuous external supply of zinc is important for metabolic needs, growth, and tissue repair that the recommended daily allowance of zinc for an average adult
male is 11mg and the requirement increases from 8 mg/d to up to 12 mg/d in females during pregnancy and location [2]. Zinc deficiency can be caused by inadequate intake, poor gastrointestinal absorption or augmented excretion that the imbalance of zinc cause diseases and promote disease progression. Zinc deficiency, either due to diminished zinc uptake in age-dependent disturbed zinc metabolism, causes impaired immune function that person who have insufficient nutritional supply of zinc are also at risk. A milder degree of zinc deficiency is a common observation in the elderly, and this marginal zinc deficiency is suspected to have clinical relevance, in which ageing is often associated with a decline in immune function, so-called immunosenesence, defined as changes occurring in all parts of the immune system with increasing age [3]. Thus, well-balanced nutritional zinc uptake can counteract the age-dependent deterioration of the immune system. In addition, the detoxification of excess zinc is essential for the synthesis of phytochelatin (PCs) that contributes significantly to the accumulation of zinc, in which PC formation is essential for Zn\(^{2+}\) tolerance and provides driving force for the accumulation of Zn [4].

On the other hand, viruses have evolved different strategies for their multiplication and propagation that more than 300 viruses are known to be pathogenic in humans and animals producing a variety of syndromes, in which viruses are still the most common agents of all human ailments. The viruses are the smallest infectious agents consisting of a single nucleic acid (RNA or DNA) encased in a protein shell, which may be covered with a lipid-containing membrane. Animal viruses may infect host cells by anchoring to an appropriate receptor molecule, which will trigger penetration of the entire virion or some of its components, always including the viral genome, into the cell. Viruses are the smallest infectious agents containing only one type of nucleic acid (DNA or RNA) covered by a protein coat, which may be surrounded by a lipid-containing membrane. A virion is composed of viral proteins, nucleic acid, lipids and carbohydrates. The structural proteins of viruses protect the viral genome, participate in attachment of virus to a susceptible cell, facilitate transfer of viral nucleic acid from one host cell to another and are antigenic determinants of the virus [5].

These include not only structural proteins forming icosahedral capsids and other components of virus particle, such as proteins of cylindrical viruses or different components of tailed phages, but also many viral enzymes such as viral proteinases, and RNA and DNA polymerases. The most important factor in a virus is genomic alternations that the factors in the host mostly depend upon the nutritional status and the optimum functioning of the immune system [6]. The life cycle of a virus and may be cell death, in which at any of these steps the life cycle of the virus can be aborted by various body mechanism, mainly by the immune response [6]. In this review article, firstly, anti-bacterial activity of zinc ions, zinc and viral infection, and viral life cycle are described. Secondly, ant-viral activities of ZnO and zinc finger protein are dealt with virus-host interaction, viral pathogenesis, and antiviral approaches. Lastly, it is to determine the antiviral activities of Zn\(^{2+}\) ions along viral life cycle with viral replication, viral RNA degradation, and ROS generation and oxidative stress.

2. ANTI-BACTERIAL EFFECT OF Zn\(^{2+}\) ION SULFATE SOLUTIONS

Halo inhibitory susceptibility tests are carried out for nitrate and sulfate solutions against *Staphylococcus epidermidis*, in which relationship between Al\(^{3+}\), Zn\(^{2+}\), Cu\(^{2+}\), and Ag\(^{+}\) ions and halo-inhibitory zone size is indicated in Fig. 1. It has been found that the
antibacterial effect for zinc ions was the highest in the sulfate solution system, due to the largest halo-inhibitory zone observed in Zn$^{2+}$ ion solution. In this study, considering such as the highest antibacterial activity for Zn$^{2+}$ ions obtained from halo inhibitory tests of metallic sulfate solutions, the processes of bacteriolyses and destructions by antibacterial activities of Zn$^{2+}$ ions are analyzed and considered against thick peptidoglycan (PGN) layer cell wall, and outer membrane-connecting thin PGN layer cell wall [7,8]. In regulation of viral growth, as is distinct from bacterial cell death, Zn$^{2+}$ ions play great roles and treatments for both host cell and virus strand as to host-cell and virus death, since viruses must be living within host-cell.

![Figure 1. Relation of metals ion in the nitrate and the sulfate aqueous solutions (metallic ion concentration of 100 mM/L) and halo inhibitory zone (in mm) against Staphylococcus epidermidis](image)

Hence, this, together with the previously gathered broad knowledge of the role of Zn$^{2+}$ as a cofactor of viral proteins, suggests that the accessibility of zinc ions in infected cells could be a potentially limiting factor during virus life cycle, interplaying between cellular zinc ions and viruses growth, as is distinct from bacterial cell death, Zn$^{2+}$ ions play great roles and
treatments for both host cell and virus strand as to host-cell and virus death, since viruses must be living within host-cell. Hence, this, together with the previously gathered broad knowledge of the role of \( \text{Zn}^{2+} \) as a cofactor of viral proteins, suggests that the accessibility of zinc ions in infected cells could be a potentially limiting factor during virus life cycle, interplaying between cellular zinc ions and viruses.

3. A COMPLEX INTERACTION OF ZINC AND VIRAL INFECTIONS

The commonest metal to bind with a virus-protein is zinc that is the second most abundant trace metal found in eukaryotic organism, second only to iron, zinc is required for essential catalytic functions in more than 300 enzymes, stabilization and induction of the folding of protein subdomains. \( \text{Zn}^{2+} \) ions are integral part of some viral proteins and play an important role in their survival and pathogenesis. A number of trace metals are essential micronutrients and their deficiency and infection diseases often coexist and exhibit complex interactions that deficiency of trace metals is known to alter the genome of the viruses and the grave consequences of this may be the emergence of new infections [9].

Zinc finger (ZF) that is small protein domains in which zinc plays a structural role contributing to the stability of the domain and is small DNA-binding peptide motifs. Zinc ions has a higher affinity for a protein ligand and strongly prefers a tetrahedral geometry that rigid \( \text{Zn}^{2+} \)-binding sites appear to be more selective than \( \text{Mg}^{2+} \)-binding sites, and a protein can generally select \( \text{Zn}^{2+} \) against the background of a much higher \( \text{Mg}^{2+} \) concentration [9].

In HIV, serum level of zinc is frequently diminished, zinc deficiency is the most prevent micronutrient abnormality seen in HIV infection, in which low levels of plasma zinc predict a three-fold increase in HIV-related mortality, whereas normalization has been associated with significantly slower disease progression and a decrease in the rate of opportunistic infection [6]. The replication process of HIV requires a number of nucleic acid annealing steps facilitate by the hybridization and helix-destabilizing activities of HIV nucleocapsid (NC) protein. Zinc deficiency characterized by low plasma zinc levels over time enhances HIV-infected drug users that the amount of zinc supplementation in HIV infection appears to be critical, because deficiency, as well as excessive dietary intake of zinc, have been linked with declining CD4 cell counts and reduced survival, in which it is needed to determine the optimal zinc supplementation level in HIV-infected patients.

The HIV-1 transcriptional regulatory protein, Tat is a pleiotropic factor that represses expression of the human manganese-superoxide dismutase that Tat increases oxidative stress as shown by decreased glutathione and NADPH levels [6]. These changes enhance proliferation and apoptosis and alter the activity of zinc thiolate containing proteins such as Sp-1 that the zinc chelator TPEN sensitizes HeLa-tat cells to apoptosis which in these cells binding of the zinc-containing factor Sp1 to its DNA sequence is higher than in parental cells [6]. The integration of all of these findings from seemingly distinct fields led to the discovery of a previously unknown type of host-virus interaction, showing that the mechanisms controlling cellular \( \text{Zn}^{2+} \) trafficking constitute natural antiviral barriers.

This, together with the previously gathered broad knowledge of the role of \( \text{Zn}^{2+} \) as a cofactor of viral proteins, suggests that the accessibility of zinc ions in infected cells could be a potentially limiting factor in the virus life cycle [10].
4. VIRAL LIFE CYCLES

Enveloped HIV viral life cycle is involved from ① Binding (Attachment, Virus Entry): HIV binds to receptors on the surface of a CD4 cell, ② Fusion (Endocytosis): The HIV envelope and the CD4 cell membrane fuse, which allows HIV to enter the CD4 cell, ③ Reverse Transcription: inside the CD4 cell, HIV releases and uses reverse transcriptase to convert its genetic material-HIV RNA into HIV DNA. The conversion of HIV RNA to HIV DNA allows HIV to enter the CD4 cell nucleus and combine with the cell’s genetic material-cell DNA, ④ Integration (Translation and Polypeptide processing): Inside the CD4 cell nucleus, HIV releases integrase of an HIV enzyme. HIV uses integrase to insert its viral DNA into the DNA of the CD4 cell, ⑤ Replication (RNA replication): Once integrated into the CD4 cell DNA, HIV begins to use the machinery of the CD4 cell to make long chains of HIV proteins. The protein chains are the building blocks for more HIV, ⑥ Assembly (Virion assembly): New HIV proteins and HIV RNA move to the surface of the cell and assemble into immature noninfectious HIV, and ⑦ Budding (Virion release): Newly formed immature (noninfectious) HIV pushes itself out of the host CD4 cell. The new HIV releases protease of a HIV enzyme. Protease acts to break up the long protein chains that form the immature virus. The smaller HIV proteins combine to form mature infectious HIV [11]. Distinct roles along the viral life cycle is that the viral protein R(Vpr) of HIV-1 has been shown to play multiple functions with an effect on the accuracy of the reverse-transcription process, the nuclear import of the viral DNA as a component of the pre-integration complex, cell cycle progression, regulation of apoptosis, and the transactivation of the HIV-LTR as well as host cell genes [12]. Hepatitis C virus (HCV) is a hepatotropic RNA virus of the genus Hepacivirus that the recent HCV therapeutic development has been greatly enhanced by basic understanding of HCV virology and life cycle, through studies using HCV cell culture systems and replication assays [13]. Each of these steps of HCV life cycle such as viral attachment, entry, fusion, viral RNA translation, posttranslational processing, HCV replication, viral assembly and release provides potential targets for novel antiviral therapeutics to cure HCV infection and prevent the adverse consequences of progressive liver disease [13].

The other, non-enveloped HAV viral life cycle is involved in ① Receptor Binding, ② RNA Uncoating, ③ Translation and Proteolytic Processing, ④ RNA Replication, ⑤ Virion Assembly, and ⑥ Maturation and Release [14]. Unlike other picornaviruses, hepatitis A virus (HAV) replicates so inefficiently in cell culture that the study of its RNA biosynthesis presents a major experimental challenge that the replication capacity of the HAV replicon was clearly demonstrated by its ability to recombine genetically with a non-viable, full-length HAV genome that served as capsid donor and thus to rescue a fully infectious virus [15]. Hence, it becomes clear that autonomous HAV RNA replication does not require sequence for the HAV structural proteins; and that low- with non-viable genomes [15]. Thus, the course of the life cycles of viral infections is governed by complex interactions between the virus and the host cellular system. Viruses depend on a host cell for their protein synthesis that the virus must first bind to the host cell, and then the virus or its genome enters in the cytoplasm, in which the genome is liberated from the protective capsid and, either in the nucleus or in the cytoplasm. It is transcribed and viral mRNA directs protein synthesis, in a generally well regulated fashion. Finally, the virus undergoes genome replication and together with viral structural proteins assembles new virions which are then released from the cell that
viral attachment or entrance have proved to be difficult to be discovered, entry inhibitor has been proved in which this is enfuvirtide, a synthetic peptide that targets the HIV gp41 envelope protein to prevent fusion.

5. ZnO INHIBITS VIRAL ACTIVITY

Zinc oxide tetrapods (ZnOTs) with micro-nanostructures synthesized by flame transport, approach significantly blocking of Herpes simplex virus type-2 (HSV-2) entry into target cells, and, in addition, demonstrate the potential to stop the spread of the virus among already infected cells that effective blocking of first step of HSV-2 pathogenesis is verified significant prophylactic effects against the viral disease; any in vitro therapeutic effects of blocking this interaction [16]. The ZnOTs exhibit the ability to neutralize HSV-2 virions that natural target cells such as human vaginal epithelial and HeLa cells showed highly reduced infectivity when infected with HSV-2 virions that were pre-incubated with the ZnOTs, in which the mechanism behind the ability of ZnOTs to prevent, neutralize or reduce HSV-2 infection relies on their ability to bind the HSV-2 virions [16]. Thus, the observed results demonstrate that blocking HSV-2 attachment can have prophylactic as well as therapeutic application. Furthermore, Zinc oxide tetrapod nanoparticles(ZOTEN) provide adjuvant benefits in combination with the captured virions for induction of protective immunity against genital herpes, inhibit the spread of newly produced HSV-2 by trapping them, provide the directly therapeutic aspects and more information on versatile use of ZOTEN to control persistent infections [17]. Zinc oxide tetrapods inhibit herpes simplex virus 1(HSV-1) infection of a member of the Alphaherpesvirinae subfamily that contains a double-stranded linear DNA genome, which is encapsulated by a protein capsid and a host-derived envelope [18]. The ability to visualize HSV-1 growth and spread in corneal tissues can provide new details about HSV-1 infection of the cornea and efficacy of new cornea-specific antiviral drug candidates, in which the model was used to visualize and study HSV-1 entry and spread of the infection in tissue [18].

6. ANTIVIRAL ACTIVITIES OF ZINC FINGER PROTEIN

All retroviral nucleocapsid (NP) proteins (except those of spumaretroviruses) that contain one or two copies of the conserved sequence motif C-X$_2$-C-X$_4$-H-X$_4$-C, where C is cysteine, H is histidine, and X represents other amino acids which differ in different retroviruses. The conserved cysteine and histidine residues coordinate a zinc ion in each such motif [19]. Zinc finger reactive compounds reacted with the zinc finger in the viral nucleocapsid (NC) protein inactivate murine leukemia virus (MuLV). Zinc fingers are the targets for inactivation of MuLV and HIV-1 by the compounds, in which the absolute conservation of the zinc finger motif among oncoretroviruses and lentiviruses and the lethality of all known mutations altering the zinc-binding residues suggest that only the normal, wild-type structure can efficiently perform all of its functions [19]. This possibility would make the zinc finger an ideal target for antiretroviral agents. Mutagenesis studies have shown that retroviral NC protein Zn$^{2+}$ fingers (-Cys-X-Cys-X$_4$-His-X$_4$-Cys-[CCHC]) perform multiple functions in the virus life cycle that Moloney murine leukemia virus (Mo-MuLV) mutants

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His34→Cys (CCCC) and Cys39→His (CCHH) were able to package their genomes normally but were replication defective, in which the CCCC and CCHH mutants produced these DNA copies at greatly reduced levels [20]. Thus, strict conservation of the CCHC structure in NC is required for infection events prior to and possibly including integration, in which is characterized by the block in replication of NC protein zinc finger mutants from Mo-MuLV [20]. The NC protein of HIV-1 has two zinc fingers, each containing the invariant metal ion binding residues CCHC that mutations in the CCHC motifs are deleterious for reverse transcription, in which the zinc fingers contribute to the role of NC in complete tRNA primer removal from minus-strand DNA during plus-strand transfer [21].

Thus, it appears that zinc finger interactions are important components of NC nucleic acid chaperone activity. In the minus-strand transfer step of HIV-1 reverse transcription, the NC promotes annealing of the 3’-‘R’ (repeat) region of the RNA genome to its complementary sequence located in the newly synthesized minus-strand strong-stop DNA, in which the R region contains the highly stable transactivation response (TAR) RNA hairpin [22]. A specific zinc finger architecture is required for optimal TAR RNA binding and helps to explain the requirement for the zinc finger motifs of NC in its role as a nucleic acid chaperone in minus-strand transfer [22]. The zinc finger antiviral protein (ZAP) is isolated host antiviral factor that it specifically inhibits the replication of Mo-MLV and Sindbis virus (SIN) by preventing the accumulation of viral RNA in the cytoplasm [23].

The CCCH zinc finger motifs of ZAP play important roles in RNA binding and antiviral activity, in which disruption of the second and fourth zinc fingers abolished ZAP’s activity, whereas the disruption of the first and third fingers just slightly lowered its activity [23]. Zinc finger reactive compounds also inactivate respiratory syncytial virus (RSV) in the nucleocapsid proteins (NC) that are also effective against RSV, in which AT-2-inactivated RSV vaccine is not strongly immunogenic in the absence of adjuvants [24]. In adjuvanted form, vaccine induces immunopathologic response in which the mere preservation of surface antigens of RSV, therefore may not be sufficient to produce a highly-efficacious inactivated virus vaccine that does not lead to an atypical disease [24]. The ZAP was originally identified as a host factor that inhibits the replication of Mo-MLV. But, here ZAP can inhibit HIV-1 infection by recruiting both the 5’ and 3’ mRNA degradation machinery to specifically promote the degradation of multiply spliced HIV-1 viral mRNAs [25].

Inhibition of Glycogen synthase kinase 3β (GSK3β) by inhibitor SB216763 or down-regulation of GSK3β by RNAi reduced the antiviral activity of ZAP, in which phosphorylation of ZAP by GSK3β modulates ZAP activity [26]. ZAP also inhibits expression of murine gammaherpesvirus 68 (MHV68) M2 that plays important roles in establishment and maintenance of viral latency, in which downregulation of endogenous ZAP in cells harboring latent MHV-68 promoted lytic replication of the virus [27]. The ZAP is a mammalian host restriction factors that inhibits the replication of a variety of RNA viruses, including retroviruses, alphaviruses and filoviruses, through interaction with the ZAP-responsive elements (ZRE) in viral RNA, and recruiting the exosome to degrade RNA substrate, in which the two isoforms of human ZAP inhibit HBV replication in human hepatocyte-derived cells through posttranscriptional down-regulation of viral pgRNA. Thus, ZAP is intrinsic host antiviral factor with activity against HBV through down-regulation of viral RNA, and ZAP plays a role in the innate control of HBV replication that shed light on virus-host interaction, viral pathogenesis, and antiviral approaches [28].
Plant viruses cause a variety of diseases and in susceptible hosts. It has been investigated that an RNA virus-encoded zinc-finger protein acts as a plant transcription factor and induces a regulator of cell size and proliferation in two Tobacco Species [29]. The results establish the role of the p12 protein in modulation of host cell morphogenesis, that other members of the conserved C-4 type ZF family of viral proteins instigate reprogramming of plant development by mimicking eukaryotic transcriptional activators [29]. Tripartite motif-containing protein 25 (TRIM25) has the factor contributing most to the antiviral function of ZAP that is critical for ZAP’s ability to inhibit translation of the incoming SINV genome as a bona fide ZAP cofactor, in which the TRIM25 leads to increased ZAP modification enhancing its translational inhibition activity [30].

7. MOLECULA DEVELOPMENT OF ANTIVIRAL AGENTS AS VIRAL AND CELLULAR TARGETS

Anti-HIV-1 therapy has been developed for use in humans and the progression from monotherapeutic treatment regimens to today’s highly active combination antiretroviral therapies has had a dramatic impact on disease progression in HIV-1-infected individuals. In spite of the success of AIDs therapies and the existence of inhibitors of HIV-1 reverse transcriptase, protease, entry and fusion, and integrase, the identification of new and novel viral and cellular targets for therapy are still necessary that antiretroviral therapeutic strategies and the development of novel strategies are ongoing, and has been under the progression of antiviral inhibitor as targeting viral enzymes and cellular host factors involved in the viral life cycle [31]. During a virus infection, reprogramming of the host cell occurs for mainly two reasons [32]. First, the virus needs to establish optimal conditions for replication to ensure efficient production of progeny virus, secondly, the virus must interfere with the host cell antiviral defense mechanisms to maximize the likelihood of escape and spread of the progeny virus. Hence, it is necessary to understand the interaction between the virus and it host cell that most of the extensive knowledge about viral products and their potential activities stems from the analysis of individual genes. So far, less is known about their relevance for the interaction between virus and host cell during the infection [32]. The obtained results have shown that expression of a limited number of genes was modulated during infection of HeLa cells, and that significantly, adenovirus consistently targeted genes involved in regulation of cell growth and antiviral defense. However, it is found that half of the regulation of genes to encode proteins related to metabolic pathways or cell structures in which the relevance of modulating these genes has only been addressed briefly, and additional experiments are required to determine whether these events are initiated directly by viral factors or constitute host cell responses or indirect effects of yet unknown importance [32]. During virus infection, there are virus-specific processes within the virus replicative cycle or virus-infected cell that attractive targets for chemotherapeutic intervention such as virus adsorption and entry into the host-cell, reverse RNA→DNA transcription, viral DNA polymerization, and cellular enzymatic reactions that are associated with viral DNA and RNA synthesis and viral mRNA maturation (i.e. methylation). Chemotherapeutic agents, both nucleoside(and nucleotide) and non-nucleoside entitles, have been identified that specifically interact with these viral targets that selectively inhibit virus replication and that are used for clinical use in the treatment of virus infections in humans [33].
8. PREVENTION OF VIRUS INFECTION

Prevention of virus infections is a major objective in agriculture and human health. One attractive approach to the prevention is inhibition of virus replication that to demonstrate this concept, an artificial zinc finger protein (AZP) targeting the replication origin of the Beet severe curly top virus (BSCTV), a model DNA virus, was created [34]. Since the mechanism of viral DNA replication is well conserved among mammals and plants, this approach could be applied not only to agricultural crop protection but also to the prevention of virus infections in humans [34].

9. PREVENTION OF VIRUS ADSORPTION/ENTRY/FUSION

The inactivated virus is defective in the glycoprotein-dependent functions of penetration and, to some extent, adsorption by zinc sulfate (15 mM-ZnSO₄) [35]. Entry of the virus into the host cell is mediated by the viral envelope glycoprotein (GPC). It is likely that for zinc-binding domain in the Junin virus envelope glycoprotein, the zinc-mediated anchoring of stable signal peptide (SSP) contributes to positioning the ectodomain loop of SSP relative to the G2 ectodomain to modulate membrane fusion. Small molecule compounds that target the pH-sensitive SSP-G2 interface in the ectodomain of GPC have been shown to inhibit pH-induced activation of membrane fusion and prevent virus entry [36]. The coronavirus (CoV) S protein requires cleavage by host cell proteases to mediate virus-cell and cell-cell fusion which many strains of the murine coronavirus mouse hepatitis virus (MHV) have distinct, S-dependent organ and tissue tropisms despite using a common receptor, suggesting that they employ different cellular proteases for fusion [37].

Thus, the use of cellular zinc metalloproteases is effective for virus entry and coronavirus fusion. The envelope GPC of the Junin arenavirus (GP-C) mediates entry into target cells through a pH-dependent membrane fusion mechanism that these results suggest a zinc finger-like domain structure in the cytoplasmic domain (CTD) of transmembrane (G2) and propose the remaining residues in the series (His-459, Cys-467, and Cys-469) form an inter-subunit zinc-binding center that incorporates Cys-57 of SSP [38].

This unusual motif may act to retain SSP in the GP-C complex and position the ectodomain loop of SSP for its role in modulating membrane fusion activity. The alphavirus Semliki Forest Virus (SFV) enters its host cell through receptor-mediated endocytosis that this process involves binding of the virus to a cell-surface receptor and subsequent vesicular transport of intact virions to the endosomal cell compartment, in which there, induced by the mildly acidic pH in the lumen of the endosomes, fusion of the viral and endosomal membranes occurs and the viral genome gains access to the cytosol. Zn²⁺ ions inhibit specifically SFV-liposome fusion that the inhibition is the level of the fusion reaction itself, since virus-liposome binding was found to be unaffected [39,40]. Zn²⁺ is strong inhibitor of the fusion step of several alphaviruses [40]. Virus-liposome binding solely requires low-pH-induced heterodimer dissociation, while fusion depends on further rearrangements in the carrying the membrane fusion activity E1 spike protein, in which as these rearrangements occur subsequently to the binding step, their precise course, including the formation of a fusion complex, may be influenced by interaction of E1 with target membrane lipids [39]. Excess free intracellular zinc is rapidly buffered by binding to cellular proteins such as the
metallothioneins or is removed via zinc transporters [40]. Thus, the use of zinc as an inhibitor would presumably require its release only at the site of alphavirus fusion; such a delivery method would be technically challenging [40]. Bovine leukemia virus (BLV) entry into the host cell is supposed to be mediated by interactions of the extracellular envelope glycoproteins with cellular receptors that entering the host cell through interactions of envelope glycoproteins of specific cellular receptors with Zn ions leads to fusion of the virus and cell membranes and followed by delivery of the viral genome into the cytoplasm [41]. Thereby, contributing to the extracellular envelope structural integrity, interacting regions differently affect viral fusion and infectivity in vivo [41].

10. UNCOATING/BLOCKING

Enveloped virus entry at the plasma membrane includes binding of the virion to one or more receptors, changes in the virion components, membrane fusion, and membrane uncoating. Membrane uncoating will be used to represent only the separation of the virion internal contents and the viral envelope, while the term “uncoating” is sometimes used to mean the release of the viral genome from the capsid or other structures that have also entered the cell, but the term membrane uncoating will be used as to represent only the separation of the virion internal contents and the viral envelope [42]. The process of genome release or uncoating after viral entry is one of the least-studied steps in the flavivirus life cycle that flaviviruses are mainly arthropod-borne viruses, including emerging and reemerging pathogens such as dengue, Zika, and West Nile viruses, in which molecular aspects of dengue virus genome uncoating and the fate of the capsid protein and RNA genome early during infection were investigated, and found that capsid is degraded after viral internalization by the host ubiquitin-proteasome system [43]. However, proteasome activity and capsid degradation were not necessary to free the genome for initial viral translation. Genome uncoating was blocked by inhibiting ubiquitination, in which using different assays to bypass entry and evaluate the first rounds of viral translation, a narrow window of time during infection that requires ubiquitination but not proteasome activity was identified [43]. Hence, these results provide the first insights for antiviral intervention into dengue virus uncoating by Zn-binding degradation and enzyme inhibition of nucleocapsid, capsid protein, viral genome.

11. CAPSID/NUCLEOCAPSID PROTEIN/NUCLEIC ACIDS/DNA/RNA

Zinc ions inhibit virus production, procapsid synthesis and viral RNA synthesis in foot-and-mouth disease virus (FMDV) infected-BHK 21 cell that the degree of inhibition depends upon the zinc concentration and the time of addition of the drug [44]. Arenaviruses are developed viruses with a genome composed of two single-stranded RNA species, designated L (large ca.7 kb) and S (small.ca. 3.5 kb). Junin virus, a South American arenavirus, is the aetiological agent of a severe endemo-epidemic disease called Argentine haemorrhagic fever. The S RNA encodes the major structural proteins of the virion, which are the precursor of the envelope GPC and the vital nucleocapsid protein (N) [45]. N protein has two independent binding sites; the classical zinc finger and the region immediately adjacent to it. However, these two binding sites exclude one another or bind zinc simultaneously, acting as a unique
RING-finger-like structure. The relevance of these residues in zinc binding and the significance of the zinc-binding activity in the N protein interactions that lead to the formation of nucleocapsids and / or to the transcriptional antitermination activity [45]. The viral nucleocapsid protein in the HIV-1 plays seminal roles in replication, thus representing a major drug target that functions of the nucleocapsid protein rely on its two zinc-fingers and flanking basic residues [46]. Zinc ejectors inhibit functions of nucleocapsid protein, but with limited specificity. APOBEC3A (A3, apolipoprotein B mRNA-editing, catalytic polypeptide with two Zn$^{2+}$-binding motifs) that A3 gene N-terminal domain carries determinants important for targeting the protein to viral nucleoprotein complexes (NPCs), in which transfer of this domain to A3A results in A3A targeting to viral NPCs and confers antiviral activity [47]. Murine hepatitis virus(MHV) is a positive-strand RNA virus of Coronaviridae that possess genomes of approx. 31,300 nucleotides [48]. The non-structural proteins of MHV bind zinc ions and nucleic acids that zinc fingers are known to be occasionally involved in protein-protein interaction and MHV interacts with tRNA, single-stranded RNA, double-stranded DNA as shown by gel-shift experiments [48]. Influenza viruses are enveloped viruses with a segmented negative strand RNA genome. Each vRNA segment is complexed with the major RNA-binding protein nucleoprotein and carries a copy of the polymerase complex. Intact influenza virus contained zinc and this zinc is bound to the M1 protein in the virus. A small percentage of influenza virus M1 protein that lines the inside of the viral lipid bilayer, contains zinc, in which but zinc does not influence in vitro M1-RNA interaction [49]. Thus, the RNA binding and transcription inhibition activities of various M1 proteins were determined, and it is suggested that the zinc in M1 has a structural role in the virion than nucleic acid binding.

The nucleocapsid C-terminal finger of HIV (NCp7) protein is an attractive target for antiviral drug that small molecules containing platinumated purine nucleobases mimic the natural DNA (RNA)-tryptophan recognition interaction of zinc finger peptides. Targeting retroviral Zn finger-DNA interactions represent a conceptual advance over electrophiles designed for chemical attack on the zinc finger alone [50]. These results demonstrate the examples of a new platinum structural class targeting specific biological processes, distinct from the bifunctional DNA-DNA binding of cytotoxic agents like cisplatin and confirm also the validity of a chemical biological approach for metallodrug design for selective ternary DNA(RNA)-protein interactions [50]. Hepatitis B virus (HBV) DNA for cleavage using zinc finger nucleases(ZFNs) have been targeted, which cleave as dimers that co-transfection of ZFN pair with a target plasmid containing the HBV genome resulted in specific cleavage [51]. Thirteen of 16 clones sequenced contained frameshift mutations that would lead to truncations of the viral core protein. These results demonstrate, for the first time, the possibility of targeting episomal viral DNA genomes using ZFNs [51].

12. GENOME REPLICATION

Zn$^{2+}$ is an important cofactor of many vital proteins, and Zn ions could change the activities of different transcription factors and thus, the expression patterns of cellular and viral genes. Addition of zinc chloride to chicken embryo fibroblasts infected with Sindbis virus inhibited viral particle release from the cells and the production of infectious virus, in which correlated with this inhibition was a block in the formation of viral glycoproteins and
the accumulation of larger molecular weight polypeptide precursors for these proteins [52]. The influenza virus matrix protein (M1), the most abundant protein in virus particles, plays a critical role in many aspects of virus replication, from virus entry and uncoating to assembly and budding of the virus particle. A cysteine and histidine (CCHH) motif has been proposed as a putative zinc finger motif and zinc-binding activity has been implicated in virus uncoating as well as transcription inhibition and mRNA regulation. Mutant viruses containing an alanine replacement of the cysteine and histidine residues, either individually or in combination, were seen to exhibit wt phenotype in multiple virus growth cycles and plaque morphology [53]. CCHH motif does not provide a critical function in the influenza virus life cycle in cell culture and the zinc-binding function may not be involved in virus biology. However, the lethal phenotype of the Ala mutation shows that the H9 region of M1 provides some other critical functions in virus replications [53].

Zinc supplementation decreases the morbidity of low respiratory tract infection in pediatric patients in the developing world. Hence, in vitro inhibitory effect of three zinc salts on the replication of respiratory syncytial virus (RSV) at various concentrations of 10 and 1 mM and 100 and 10μM had been examined [54] that at lowest concentration, zinc was present during preincubation, adsorption, penetration, or egress of virus [54]. Thus, RSV plaque formation was prevented by pretreatment of Hep-2 cell monolayer cultures with zinc or by addition of zinc to methylcellulose overlay media after infection, in which zinc mediates antiviral activity on RSV by altering the ability of the cell to support RSV replication. Artificial zinger proteins (AZPs) also inhibit virus DNA replication [31]. Human rhinoviruses (HRVs) are the most frequent cause of the common cold and are implicated in more than 50% of upper respiratory tract infections that the viruses have a single-stranded positive-sense RNA genome of approximately 7,400 nucleotides [55]. Pyrrolidine dithiocarbamate (PDTC) as binding with metal ions, is an antiviral compound that was shown to inhibit the replication of HRVs, poliovirus, and influenza virus, in which the metal ions play a pivotal role in the inhibition of virus multiplications and PDTC inhibits the activity of the viral proteases in a metal ion dependent way [55].

Increasing the intracellular Zn$^{2+}$ concentration with zinc-ionophores like pyrithione (PT) can efficiently impair the replication of a variety of RNA viruses, including poliovirus and influenza virus, in which the combination of Zn$^{2+}$ and PT at low concentration inhibits the replication of SARS coronavirus (SARS-CoV) and equine arteritis virus (EAV) in cell culture [56]. Zn$^{2+}$ directly inhibited the in vitro activity of both nidovirus polymerases, and Zn$^{2+}$ blocked the initiation step of EAV RNA synthesis, whereas in the case of the SARS-CoV RdRp elongation was inhibited and template binding reduced. Thus, the inhibitory effects of Zn$^{2+}$ chelating could be reversed, which provides the molecular mechanism details of nidovirus replication and transcription [56].

Human immunodeficiency virus reverse transcriptase (HIV-RT) like other RTs, possess both nucleotide polymerization and ribonuclease H (RNase H, activity that degrades RNA which is part of an RNA-DNA hybrid) capabilities. Several physiologically relevant cations including Ca$^{2+}$, Mn$^{2+}$, and Zn$^{2+}$ have been shown to inhibit HIV reverse transcriptase (RT), presumable by competitively displacing one or more Mg$^{2+}$ ions bound to RT that processivity (average number of nucleotides incorporated in a single binding event with enzyme) during reverse transcription was comparable with Zn$^{2+}$ and Mg$^{2+}$, and single RT molecules were able to continue extension in the presence of Zn$^{2+}$ for several hours on the same template [57].
Zn$^{2+}$ inhibition is not due to catalysis blockage but to the formation of a highly stable, kinetically diminished complex, which HIV-RT is inhibited by low Zn$^{2+}$ concentrations presenting an avenue for future drug research [57].

13. ASSEMBLY

The genome of rotaviruses is composed of 11 segments of double-stranded RNA for single proteins that six structural proteins participate in the architecture of the virus of VP1, VP2, VP3, VP4, VP6, and VP7 in which VP2 forms the internal layer of the virion, VP6 forms the middle one, and VP7 and VP4 form the external one [58]. Zinc ion is not essential for either trimerization of VP6 or transcription activity that the sensitivity of mutant VP6 proteins to proteases is strongly increased, in addition although they self-assemble into helical and spherical particles, the small helical assemblies having a diameter of 45 nm are not formed. Wild-type VP6 depleted of zinc with a metal-chelating agent is more sensitive to protease activity and does not form small helical particles. Zinc is not necessary for the transcription activity, in solution, VP6 trimers present a structural flexibility that is controlled by the presence of a zinc ion [58]. Thus, a zinc ion controls assembly and stability of the major capsid protein of rotavirus.

14. RELEASE OF VIRIONS

Interactions between viral and cellular protein are required for virus entry, replication, or egress from the cells that these interactions are facilitated by peptide sequences of domains. Viruses recruit endosomal sorting complexes required for the transport pathway to egress from the cell, which leads to virus budding which viruses utilize peptide sequences of domains to egress from host cells [59]. Targeting L-domain-dependent recruitment of host cells shows depletion of viral egress for RNA viruses. From the effect of zinc on influenza virus induced apoptosis in cultured HeLa cells [60], in HIV-1-infected U1 cells, disulfade-substituted benzamides (DIBAs) among zinc finger has inhibited the release of infectious virions, and even under conditions in which noninfectious virion particles were produced, which viral release by zinc inhibition remains unclear.

15. VIRUS RESTRICTION FACTOR; RNA DEGRADATION AND HOST-CELL DEFENSE

Virus restriction factors may be in presence of viral entry, viral DNA synthesis, intracellular movement of viral nucleic acids and viral gene expression. These restriction systems constitute newly appreciated components of an innate immunity that may be important for survival of a host exposed to virus infections [61]. One of these restriction systems is selectively degradation of viral mRNA. The kinetics of cellular mRNA decay in influenza virus-infected cells have been studied [62], in which the synthesis of the cellular proteins was reduced, showing kinetics paralleling those of mRNA decay that influenza virus
infection induces the destabilization of mRNAs and that this mRNA degradation is, at least in part, responsible for cellular protein synthesis shutoff.

The other, ZAP is a host antiviral factor that specifically inhibit the replication of certain viruses, including HIV-1, Sindbis virus, and Ebola virus. ZAP binds directly to target mRNA, and it represses the translation and promotes the degradation of target mRNA. ZAP was originally identified as a host factor that inhibits the replication of many viruses by preventing the accumulation of viral mRNAs in the cytoplasm. ZAP specifically binds to the viral mRNA and recruits the cellular RNA degradation machinery to degrade the target RNA which for viruses to escape ZAP-specific viral mRNA degradation, one intriguing possibility is that viruses might encode factors that either inactivate ZAP or block ZAP-mediated RNA degradation [63]. In general, RNA is degraded at the end of its useful life, which is long for a ribosomal RNA but very short for excised introns or spacer fragments that is closely regulated for most mRNA species. RNA molecules with defects in processing, folding, assembly with proteins are identified and rapidly degraded by the surveillance machinery [64]. The degradation is mediated by the viral RNA polymerase that associates with host RNA polymerase II (Pol II) that increased ubiquitylation of Pol II in infected cells and upon the expression of the viral RNA polymerase suggesting that the proteasome pathway plays a role in Pol II degradation [65].

ZAP also inhibits HIV-1 infection by promoting the degradation of specific viral mRNAs that overexpression of ZAP rendered cells resistant to HIV-1 infection in a ZAP expression level-dependent manner, whereas depletion of endogenous ZAP enhanced HIV-1 infection [66]. Thus, depletion of each of these mRNA degradation enzymes reduced ZAP’s activity and ZAP inhibits HIV-1 by recruiting both the 5’ and 3’ mRNA degradation machinery to specifically promote the degradation of multiply spliced HIV-1 mRNAs. Zinc mesoporphyrin (ZnMP) selectively and markedly down-regulated nonstructural 5A(NS5A) protein levels by increasing degradation of NS5A protein that ZnMP may hold promise as a novel agent to treat HCV infection [67]. TRIM25 also is required for the antiviral activity of ZAP that downregulation of endogenous TRIM25 abolished ZAP’s antiviral activity [68]. The TRIM25 is required for the antiviral activity of ZAP that downregulation of endogenous TRIM25 remarkably abolished ZAP’s activity. TRIM25 is required for ZAP optimal binding to target mRNA.

These results help us to better understand how the antiviral activity of ZAP is regulated, while the mechanisms by which ZAP inhibits target RNA expression have been extensively studied, how its antiviral activity is regulated is not very clear [68]. ZAP, an type1 interferon(IFN)-inducible gene, plays a critical role in elimination of Sindbis virus (SINV) that ZAP is an RNA-sensing anti-viral effector molecule which mediates the type-I-IFN-dependent host defense against SINV [69].

Several mammalian viruses encode factors that broadly dampen gene expression by directly targeting mRNA that these factors promote mRNA degradation to globally regulate both host and viral gene expression, in which in some cases, there is a lack of selectively for degradation of host versus viral mRNA, indicating that the purposes of virus-induced mRNA degradation extend beyond redirecting cellular resources towards viral gene expression [70]. In addition, several antiviral pathways use RNA degradation as a vital restriction mechanism, and these host-encoded ribonucleases target and destroy viral RNA[70]. RNA degradation in viral replication and antiviral defense leads to destroy viral RNA and restrict virus [71].
16. ROS-MEDIATED VIRUS DEATH

Table 1. Antiviral activities of \( \text{Zn}^{2+} \) ions for prevention, adsorption, entry, uncoating, replication, capsid protein, nucleic acid, assembly and release in virion proliferation

<table>
<thead>
<tr>
<th>( \text{Zn}^{2+} )</th>
<th>Antiviral activities of ( \text{Zn}^{2+} ) for prevention, adsorption/entry, uncoating, replication, assembly, and release in virus proliferation process</th>
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<tr>
<td>Prevention</td>
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<td>( \text{Zn}^{2+} )</td>
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<tr>
<td>• AZP prevents virus infection</td>
<td>• Zinc sulphate inactivates virus some extent adsorption and penetration</td>
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<tr>
<td>• 15mM-ZnSO(_4) prevent HIV infection</td>
<td>• Zinc chloride and salts: inhibition of replication</td>
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Under non-pathological conditions, cells produce reactive oxygen species (ROS) during cellular respiration that excessive ROS production and the decreased rate of its neutralization and removal by antioxidant defense mechanisms lead to an imbalance between oxidants and antioxidants which results in oxidative stress [1]. Oxidative stress is responsible for the development of many diseases. Cellular metabolisms produce different varieties of ROS as byproducts that these ROS play an important role in cell signaling and regulate hormone action, growth factors, cytokines, transcription, apoptosis, iron transport, immunomodulation, and neuromodulation, in which many retroviruses, DNA viruses and RNA viruses can cause cell death by generating oxidative stress in infected cells [72]. Further, the oxidative stress modulation in hepatitis C virus infected cells become regarding the dual functions of the oxidative stress induced by the virus and the host cell [73]. Hence, these may be possible to
establish new and more effective therapeutic targets for many virus treatments. Dengue virus-induced ROS produce iNOS (inducible nitric oxide synthase), NO release, and the response to the iron chelator that NO inhibits RNA virus replication that NO is known as an antiviral molecule [74]. The other, zinc has several antioxidant effects that it is a cofactor of the Cu/Zn-superoxide dismutase (SOD) enzyme which catalyzes the dismutation of superoxide radical (‘$\cdot$O$_2^-$’) into the less O$_2$ and H$_2$O$_2$. Higher pathogenic H5N1 infections are often accompanied by excessive pro-inflammatory response, high viral titer, and apoptosis that the pathogenesis of influenza virus infection is also related to oxidative stress [75]. Forced SOD overexpression can disrupt H5N1 replication in A549 cells that this behavior may be attributed to the antioxidant role of SOD; virus-induced apoptosis, pro-inflammatory response, and H5N1 infection-induced mitochondrial dysfunction.

As above-mentioned, antiviral activities of Zn$^{2+}$ ions along the viral life cycle are summarized in Table 1 that shows viral prevention, adsorption and entry, uncoating, replication, capsid protein, DNA/RNA, assembly and budding in viral proliferation process.

16. CONCLUSIONS

Zinc is involved in many metabolic and chronic diseases such as diabetes, cancer, neurodegenerative diseases, whereas there is also strong establishment between zinc deficiency and several infections such as malaria, HIV, tuberculosis, measles, and pneumonia. In zinc homeostasis, ZIP and ZnT show tissue specificity and developmental and stimulus responsive expression patterns. Zinc ions has a higher affinity for a protein ligand and strongly prefers a tetrahedral geometry that rigid Zn$^{2+}$-binding sites appear to be more selective than Mg$^{2+}$-binding sites. The replication process of HIV requires nucleic acid annealing steps facilitate by the hybridization and helix destabilizing activities of HIV nucleocapsid (NC) protein. The course of the life cycles of viral infections is governed by complex interactions between the virus and the host cellular system. Viruses depend on a host cell for their protein synthesis that the virus must first bind to the host cell, and then the virus enters in the cytoplasm which the genome is liberated from the protective capsid and, either in the nucleus or in the cytoplasm. The use of cellular zinc metalloproteases is effective for virus entry and coronavirus fusion.

The process of uncoating after viral entry is one of the least-studied steps in the flavivirus life cycle that flaviviruses are mainly arthropod-borne viruses, including emerging and reemerging pathogens such as dengue, Zika, and West Nile viruses, in which molecular aspects of dengue virus genome uncoating and the fate of the capsid protein and RNA genome early during infection were investigated, and found that capsid is degraded after viral internalization by the host ubiquitin-proteasome system. However, proteasome activity and capsid degradation were not necessary to free the genome for initial viral translation. Genome uncoating was blocked by inhibiting ubiquitination, in which using different assays to bypass entry and evaluate the first rounds of viral translation, a narrow window of time during infection that requires ubiquitination but not proteasome activity was identified. Hence, these results provide the first insights for antiviral intervention into dengue virus uncoating by Zn$^{2+}$-binding degradation and enzyme inhibition of nucleocapsid, capsid protein, viral genome. Artificial zinger proteins also inhibit virus DNA replication. Human rhinoviruses are the most frequent cause of the common cold and are complicated in more than 50% of upper
respiratory tract infections that the viruses have a single-stranded positive-sense RNA genome of approximately 7,400 nucleotides. Pyrrolidine dithiocarbamate (PDTC) as binding with metal ions, is an antiviral compound that was shown to inhibit the replication of HRVs, poliovirus, and influenza virus. Increasing the intracellular Zn$^{2+}$ concentration with zinc- ionophores like pyrithione (PT) can efficiently impair the replication of a variety of RNA viruses. Zn$^{2+}$ directly inhibited the in vitro activity of both nidovirus polymerases, and Zn$^{2+}$ blocked the initiation step of EAV RNA synthesis, whereas in the case of the SARS-CoV RdRp elongation was inhibited and template binding reduced. HIV reverse transcriptase (HIV-RT) like other RTs, possess both nucleotide polymerization and ribonuclease H (RNase H, activity that degrades RNA which is part of an RNA-DNA hybrid) capabilities.

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Cellular metabolisms produce different varieties of ROS as byproducts that these ROS play an important role in cell signaling and regulate hormone action, growth factors, cytokines, transcription, apoptosis, iron transport, immunomodulation, and neuro-modulation, in which many retroviruses, DNA viruses and RNA viruses can cause cell death by generating oxidative stress in infected cells. Oxidative stress is responsible for the development of many diseases. Dengue virus-induced ROS produce inducible nitric oxide synthase (iNOS), NO release, and the response to the iron chelator that NO inhibits RNA virus replication that NO is known as an antiviral molecule. Zinc has several antioxidant effects that it is a cofactor of the Cu/Zn-superoxide dismutase (SOD) enzyme which catalyzes the dismutation of superoxide radical (•O$_2^-$) into the less O$_2$ and H$_2$O$_2$. Higher pathogenic H5N1 infections are often accompanied by excessive pro-inflammatory response, high viral titer, and apoptosis that the pathogenesis of influenza virus infection is also related to oxidative stress.

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