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Review Article

Herpes/SARS-CoV-2 Treatment with Micellized Nutraceuticals

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Abstract

In natural immunity, infected cells express part of the viral protein on their cell surface. The host's natural killer cells (NKC) recognize and directly kill the infected cells. Therefore, an antiviral drug can block any virus' steps to reproduce itself. Using the NutraNanoSphere™ technology platform, a significant array of potent antivirals nutraceuticals have been incorporated into the TriAntiVP™ (antivirus and parasite) micellized formulation. These include Curcumin, Artemisinin, Bilberry, and Vitamin D_3 as core components. These supplements have little of any side effects and are good candidates to be taken on a daily basis to prevent parasitic and viral diseases. While the use of these nutraceuticals has been hindered therapeutically because of their low aqueous solubility and rapid degradation in the stomach, the micellization process significantly increases the bioavailability.

These active supplements fight against viral disease, e.g., COVID-19 or HERPES, collectively by preventing the binding of the viral S protein to the ACE2 receptor on lung cells, thus preventing the infection process, inhibiting the protolytic processes that allow replicating viruses to leave the host cell, prevents NF-κB cytokine storm inflammatory results, inhibits viral protein processing, enables one to immediately be proactive when an initial diagnosis of a skin lesion, such as herpes, or viral illness. We think we have effective preventative formulations and treatments by combining a range of antiviral nutraceuticals to the NutraNanoSphere™ delivery system. The versatility of these treatments allows for oral medication, applying antivirals directly in the nasopharynx, and topically attacking the lesions on the skin.

Keywords: COVID-19; Immunity; NutraNanoSphere™

Introduction

The infective phase of a virus starts with the virus attaching to the host cell by a specific receptor, thus allowing access to the interior of the cell. The viral genomes are then incorporated into the host and cause the replication of the necessary building blocks for the virus to reproduce itself. In addition, the newly made virus must escape the host cell to infect more cells.

In natural immunity, infected cells express part of the viral protein on their cell surface. In addition, the host's Natural Killer Cells (NKC) recognize the infected cell as foreign and immediately destroy both the infected cells and viruses through a series of protein-based lytic mechanisms [1,2].

An antiviral drug can block any steps a virus uses to reproduce itself. For example, viral genes or proteins need to interact with various host molecules. These interactions allow antiviral drugs to mimic host molecules, interfere with the viral life cycle, and reduce its spread. As researchers build up their knowledge of viral life cycles, new antivirals may be positioned in the planning for future pandemics.

Since viruses rely on the human cell machinery to copy themselves, antiviral drug development faces the challenge of stopping the virus replication without damaging healthy cells. Scientists have found several solutions to the problem. For example, the drug Acyclovir is used to treat herpes by incorporating it into the viral polymerase and preventing the addition of any more nucleotides, thus inactivating the virus [3]. Another drug, Oseltamivir (Tamiflu) for influenza [4], acts at the stage of viral exit from the infected cell. The virus uses a key protein called neuraminidase to dissolve the cell wall and escape to infect new cells. However, Oseltamivir sticks to the neuraminidase and inhibits its enzymatic activity [4]. A third example is Zidovudine (AZT), in which AZT belongs to a group of drugs called nucleoside analogs [5]. AZT interferes with an enzyme called Reverse Transcriptase

(RT), in which HIV-infected cells make new viruses. Since AZT inhibits or reduces the activity of this enzyme, this drug causes HIV-infected cells to produce fewer viruses. However, AZT has significant side effects.

In developing antivirals, the biggest challenge is ensuring that the so-called antiviral does not hurt the host cells. An ideal antiviral drug is inert but activated by a viral protein and kills within the virus. The best antiviral is to use the God-given immune system of the NKC to kill the virus and the infected cells [1,2]. This report will use the Herpes Simplex Virus Type 2 (HSV-2) and Sars2CoV virus (COVID-19) as viral models for therapy and show the importance of natural immunity and nutraceuticals to prevent infection breakthrough by viral mutation.

Herpes Simplex Virus Type 2 (HSV-2) is one of the most prevalent sexually transmitted viruses. Heterosexual transmission in women is the fastest-growing part of the Human Immunodeficiency Virus (HIV) pandemic (UNAIDS, 2014), with 40% of global infections occurring in the female genital tract (FGT). Genital herpes is the main cause of genital ulcers worldwide; the prevalence of HSV-2 infections in the general population ranges from 10% to 60% [6-8]. Herpes viruses are DNA viruses that infect humans and animals with the ability to induce latent and lytic infections in their hosts, causing critical health complications [9,10].

Herpes viruses belong to the family of Herpesviridae, a large family of DNA viruses with severely contagious properties that use a strategy of infection known as travel and hide [11]. These viruses share the feature of forming lifelong illnesses in a latent phase with the potential of periodic reactivation. During the life cycle, herpes viruses typically infect different cell types in various tissues, and therefore, the sub-classification of these pathogens is partially based on their cell and tissue tropism [12].

For decades, integrated management of herpes virus infections has remained the main challenge in virology research. However, these infections are still incurable due to the viral latency, the problem of recurrent infections, and the resistance to antiherpetic drugs [13].

Nutraceuticals have mainly a health-supporting effect but can show their potential as drugs at higher concentrations or with improved bioavailability. As nutraceuticals have minimal or zero side effects but are able to be effective biologicals.

Our goals in using nutraceutical anti-herpes viral drugs include, in part, clinical investigations with promising levels of reduced resistance, free or minimal cellular toxicity, and diverse mechanisms of action to effectively defeat the viral infection. Challenges that hinder antiviral drug development include problems with drug resistance and recurrent infections. Therefore, this review will present important nutraceutical curative candidates against HSV-2. These include Curcumin, Bilberry, Artemisinin, and Vitamin D_3.

The use of these nutraceuticals micellized in NutraNanoSpheres™ (NNS™) to treat skin lesions topically and with oral medication is shown in Figure 1.

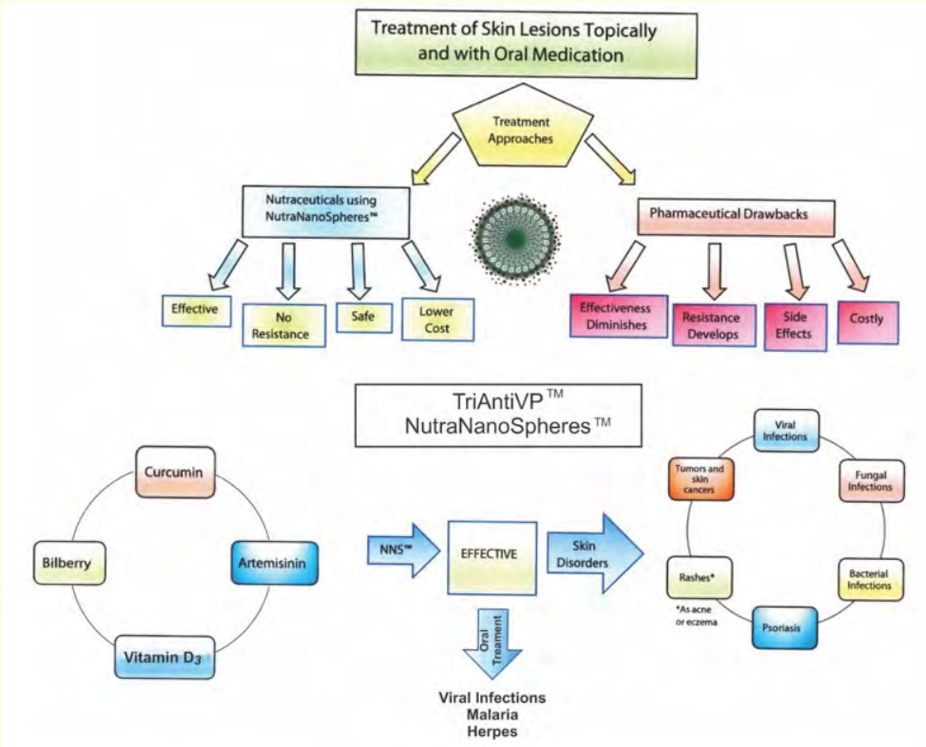

Figure 1: Treatment of Skin Lesions Topically and with Oral Medication. Advantages of treatment approaches using NutraNanoSpheres™ versus conventional pharmaceutical approaches.

However, traditional pharmaceutical treatments have serious drawbacks compared to our NNS platform. Treatment approaches using pharmaceutical drugs have the problems of diminishing effectiveness over time, resistance development, serious side effects that may occur, and the never-ending increase in costs. In addition, the NNS technology allows for the effective micellization of nutraceuticals to increase bioavailability in the bloodstream without degradation by the stomach acids. This approach allows for no resistance to develop safely and cost-effectively against the compound of interest. Since these biologicals have a long and successful history in Asian cultures, serious side effects from their applications are not expected and not known.

The antiviral compounds called TriAntiVP™ include Curcumin, Artemisinin, Bilberry, and Vitamin D_3. The applications of the NNS compounds can be taken orally and used with cotton swabs to clean the nasopharynx. They may be applied topically to treat skin cancer and microbiological infections on the skin.

Average Diameter Measurements of the NNS: In figure 2, the NNS samples were diluted by volume in a ratio of 1:6 with DI Water and filtered by a 0.45 µm Nylon membrane to remove any dust contaminants. The ZetaPALS and ZetaPlus (Malvern Instruments) were used (with a backscattering angle of 173 degrees to measure the particle size by dynamic light scattering (Particle Characterization Laboratories, Inc. Novato, CA). A non-negative least squares algorithm was used to generate the size distribution by intensity, which indicated the diameter of the major population for the TriAntiVP™ components and the TriAntiVP™ as a whole (Figure 2). The intensity data were then converted to a mass or volume distribution to compare relative amounts of each size population, which indicated the percentage of the sample represented in the respective population. The effective average diameter of 28.1 nm SD (n = 3), low polydispersity, and lack of interaction of the NNS components present the TriAntiVP™ high bioavailable micellized population that is 1/250th the diameter of a human erythrocyte.

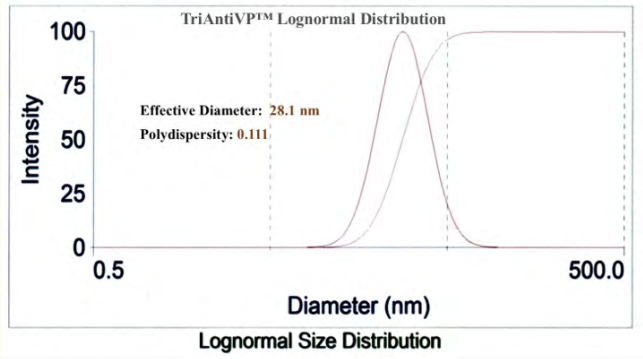

Figure 2: A non-negative least squares algorithm was used to generate the size distribution by intensity, which indicated the diameter of the major population for the TriAntiVP™ components and the TriAntiVP™ as a whole.

Herpes/SARS-CoV-2 and curcumin

Turmeric (*Curcuma longa L.*) and its active ingredient Curcumin have been extensively used as a folk medicine for its antioxidant, anti-inflammatory, and antiseptic effects, particularly in Asian countries [14]. The therapeutic efficacy and safety of Curcumin (up to 12 g/day) make it an attractive target for the prevention and treatment of different human diseases [15]. Curcumin has exhibited multiple clinical applications, including antioxidant, anti-cancer, anti-inflammatory, anti-rheumatic, antimicrobial, and hepatoprotective effects [16]. Curcumin has also been investigated for its antiviral activity against a broad spectrum of viruses such as HSV, hepatitis virus, Zika virus, influenza virus, adenovirus, and HERPES Type 2 (HSV2), and SARS-CoV-2 (COVID-19) [17]. The antiviral activity of Curcumin against COVID-19 and HSV2 could be attributed to interference with the metabolism of the virus through cell signaling and apoptosis [18]. The antiviral activity of Curcumin with the replication of the Human Immunodeficiency Virus (HIV) has been attributed to its antioxidant/anti-inflammatory roles [19]. Furthermore, Curcumin prevents the binding of the COVID-19 S protein to the ACE2 receptor on lung cells, thus preventing the infection process. Also, it inhibits the protolytic processes that allow replicating viruses to leave the host cell, prevents the NF-κB from facilitating the cytokine storm inflammatory results, and inhibits viral protein processing [20].

Curcumin may offer a viable alternative for preventing or controlling HIV replication in the female genital tract (FGT). Pre-treatment with Curcumin prevented disruption of the mucosal barrier by maintaining electric resistance across the genital epithelium. Furthermore, Curcumin pre-treatment prevents gp120- mediated upregulation of pro-inflammatory cytokines,

such as interleukin (IL)-6 and tumor necrosis factor-alpha. Curcumin also inhibits cytokines IL-8 and interferon-gamma-induced protein-10 (IP-10), which can recruit HIV target cells to the FGT. Anti-inflammatory compounds such as Curcumin may offer a viable alternative for preventing and controlling HIV replication in the FGT [21].

Furthermore, Curcumin has been shown to delay the progression of cataract development [22], protect against inflammatory markers and lipid metabolism in streptozotocin-induced diabetes, and decrease cognitive impairment in an animal model of Alzheimer's disease [23], and has have shown enhanced anti-cancer activity [24].

Herpes/SARS-CoV-2 and artemisinin

Artemisinin is a compound derived from *Artemisia annua L* with numerous anti-malaria, anti-inflammatory, antiviral, antitumor, and antimicrobial benefits [25]. Artemisinin inhibits viral replication and the release as shown with human cytomegalovirus, herpes, hepatitis B, and C viruses [26].

Artemisinin is being studied for its effectiveness against SARS-CoV-2 (COVID-19) by increasing general immunity and T-cell activity [27]. Artemisinin physically binds to COVID-19 proteins and blocks them from binding to the host receptor ACE2 [28,29]. Furthermore, Artemisinin helps regulate toll-like receptors (TLRs), which are a family of transmembrane proteins found on cells involving the host immune system or lung cells. The TLRs play an important role in identifying pathogens and directly enhance antiviral activity [30]. They can recognize patterns associated with pathogens (PAMPs) or ways related to host-derived damage (DAMPs) [31]. Additionally, TLRs can induce the production of inflammatory mediators, which are helpful when fighting off COVID-19 due to the "cytokine storm" caused by inflammatory cytokines. Artemisinin decreased TLR2 and TLR4 expression, both correlated with inflammatory properties. TLR4 specifically causes an inflammatory response because it activates the nuclear factor NF-κB, a pro-inflammatory cytokine [32]. In fact, there is even a more potent binding of Artemisinin to Lys353 and Lys31-binding hotspots of COVID-19 spike protein than hydroxychloroquine [32].

In summary, Artemisinin's anti-inflammatory benefits can fight the cytokine storm caused by the virus and downregulate the pathways the virus uses to replicate and spread.

Herpes/SARS-CoV-2 and bilberry (Bioflavonoids)

Bilberry species are known to exhibit a wide range of pharmacological activities. Bilberries are known for their exceptionally high amounts of anthocyanins with powerful antioxidant capacity. They have been shown to possess beneficial health effects, like having a protective role in cardiovascular diseases and cancer. In addition, many flavonoids also seem to have antiviral, antibacterial, antifungal, and antiallergenic properties [33]. Various studies prove that anthocyanin extracts inhibit inflammatory gene expression *in vitro* [34,35].

They have long been traditionally applied for their antiseptic, antimicrobial, cardioprotective, and antioxidant properties using the selective antiviral activity of total methanol extracts of bilberry (*Vaccinium myrtillis L.*). The antiviral effect has been tested against viruses that are important human pathogens, such as poliovirus type 1 (PV-1), coxsackievirus B1 (CV-B1), and human respiratory syncytial virus A2 (HRSV-A2), and influenza virus A/H3N2 of Orthomyxoviridae. Given the obtained results, it is concluded that bilberry is a valuable resource of antiviral substances [36].

Bilberry significantly reduced IFN-γ-induced phosphorylation of STAT1 and STAT3, thus inhibiting the mRNA expression levels and subsequent cytokine storm secretion of IL-6, TNF-α, MCP-1, and ICAM-1 with bilberry treatment. Bilberry increased mRNA expression of TNF-α and NF-κB target genes, while mRNA levels of ICAM-1 were reduced. Bilberry reduced IFN-γ-induced signal protein activation, pro-inflammatory gene expression, and cytokine secretion. Therefore, Bilberry is important in modulating inflammatory responses [37]. In addition, there is a positive relationship between antiviral activity and polyphenol content, indicating the possibility that polyphenol is one of the key factors in the antiviral effects of bilberries [38]. Finally, a correlation was found between the degree of developing resistance to disease and lack of virus accumulation in the brain, blood, spleen, and thymus showing resistance to the virus by bilberry [38].

Herpes/SARS-CoV-2 and vitamin D_3

Vitamin D_3 can reduce the risk of infections by inducing cathelicidins and defensins to lower viral replication rates and reduce pro-inflammatory cytokines [39]. Calcitriol is involved in at least 20% to 25% of the cell's gene expressions. Calcitriol is the active compound that is ultimately produced from intaking

vitamin D3. All cells of the human body have receptors for Vitamin D means calcitriol. This inflammation injures the lining of the lungs and leads to pneumonia with the increase of anti-inflammatory cytokines. Several clinical studies have shown vitamin D_3 supplementation reduced the risk of influenza [40]. Furthermore, the risk of COVID-19 infection is significantly increased during the winter months when vitamin D concentrations are lowest. Vitamin D deficiency contributes to acute respiratory distress syndrome experienced with COVID-19 [41].

The elderly population is at greater risk of developing COVID-19 and severe COVID-19, because they have lower levels of Vitamin D than younger adults. Increasing Vitamin D_3 blood levels would significantly reduce the death rate while alleviating Vitamin D deficiency [42]. Furthermore, the likelihood of developing severe COVID-19 is five-fold greater in Vitamin D deficient patients [43]. Therefore, respiratory disease mortality was statistically attributable to vitamin D insufficiency or deficiency. Vitamin D deficiency is common and accounts for a large proportion of respiratory disease mortality in older adults, supporting the hypothesis that vitamin D_3 supplementation could limit the COVID-19 pandemic [44,45].

Natural killer (NK) cells perform immunologically essential functions, such as regulating the adaptive immune response by defending against viral infection, destroying tumor cells and virally infected cells, secreting cytokines such as IFN-γ, and forming the innate immune system with dendritic cells. Vitamin D enhances innate cellular immunity by inducing antimicrobial peptides and defensins [46]. The cathelicidins derived from Vitamin D exhibit direct antimicrobial activities against a spectrum of microbes, including Gram-positive and Gram-negative bacteria, enveloped and nonenveloped viruses, and fungi [47]. The antiviral peptides produced destroy invading pathogens by compromising their cell membranes and neutralizing their biological function, thus reducing viral replication [48]. Supplementation with 4,000 IU/d of vitamin D_3 is sufficient to significantly decrease dengue virus infection [49].

Vitamin D also enhances cellular immunity by reducing the cytokine storm induced by the innate immune system. The natural immune system generates pro-inflammatory and anti-inflammatory cytokines in response to viral and bacterial infections, as observed in COVID-19 patients [50]. Vitamin D can reduce the production of pro-inflammatory Th1 cytokines, such as tumor necrosis factor α and interferon γ [51]. In addition, administering vitamin D reduces pro-inflammatory cytokines and increases anti-inflammatory cytokines by macrophages [52]. Vitamin D is a modulator of adaptive immunity [53]. Vitamin D_3 intake is formed in the following sequence: Calcitriol (Vitamin D_3) plus ultraviolet light forms Clacidiol, then Calcitriol, the active form of Vitamin D [1,25(OH)2D3]. Vitamin D suppresses responses mediated by the T helper cell type 1 (Th1) by primarily repressing the production of inflammatory cytokines IL-2 and interferon-gamma (INFγ) [54]. Additionally, Vitamin D_3 promotes cytokine production by the T helper type 2 (Th2) cells, enhancing the indirect suppression of Th1 cells by complementing this with actions mediated by several immune cell types [55].

Vitamin D_3 up-regulates the expression of NKC cytotoxicity receptors NKp30, NKp44, and NKG2D on the surfaces of NKC. These receptors also down-regulate the expression of the killer inhibitory receptor CD158 [56]. Vitamin D_3 deficiency affects T- and B-lymphocyte activation and the quantity, maturation, and function of regulatory NKC T-cells [57]. Consequently, innate and adaptive immunity become de-regulated, leading to viral infections with chronic inflammation. In addition, Vitamin D_3 supplementation helps prevent or treat chronic viral infections and even facilitates the NKCs in killing cancer cells in patients [58].

Conclusions

This review of active compounds against viral disease enables one to immediately be proactive when an initial diagnosis of a skin lesion, such as herpes, or viral illness, e.g., SARS-CoV-2 (COVID-19), is discovered. Tables 1 and 2 summarize the overview, antiviral actions against specific viruses, and the antiviral targets for the four components of TriAntiVP™ Formulation. Therefore, we believe we have an effective treatment by micellizing a range of antiviral nutraceuticals into the NutraNanoSphere™ delivery systems. In addition, we continue the development of other promising nutraceuticals, such as Ginger and mushroom derivatives as reviewed in this publication, to add to our NutraNanoSphere™ antiviral arsenal. These NNS water-soluble, high bioavailability treatments can be used in various formats. These include oral medication, intravenous delivery, as a nasal spray, or topical treatment for skin lesions.

Curcumin
Overview
Antioxidant, anticancer, anti-inflammatory, anti- rheumatic, antimicrobial, cognitive impairment, and hepatoprotective effects
AntiViral
HSV, hepatitis virus, Zika virus, influenza virus, adenovirus, and SARS-CoV-2, Human Immunodeficiency Virus (HIV), influenza A, zika, chikungunya, norovirus (HuNoV), Epstein-Barr virus(EBV) [17].
Antiviral Targets
Prevented disruption of the mucosal barrier by maintaining electrical resistance [21] expression across the genital epithelium. Prevented the gp120- mediated upregulation of pro-inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor-alpha [21]. Inhibits cytokines IL-8 and interferon gamma-induced protein-10 (IP-10), which can recruit HIV target cells [21].
Anti-inflammatory compounds such as Curcumin may offer a viable alternative for preventing and controlling HIV replication in the FGT [19].
SARS-CoV-2: prevents the binding; inhibits the entry; hinders viral genome replication and transcription; interferes with the translation and assembly [20]; prevents Cytokine Storm [32].
Artemisinin
Overview
Protecting against malaria, viruses, and cancer cells
AntiViral
Cytomegalovirus, herpes, hepatitis B, and hepatitis Cviruses26 SARS-CoV-2 (COVID-19) [27].
Antiviral Targets regulate toll-like receptors (TLRs) [30]; antiviral activity [27] by binding SARS-CoV-2 proteins and blocking binding to host ACE2 Receptor [28,29]. inhibit central regulatory processes of viral-infected cells (specifically NF-κB or Sp1-dependent pathways)and its ability to block host cells from being hijacked to replicate the virus [20]. Inhibit iNOS and COX-2 pathways, suppress ERK and NF-κB signaling, inhibit pathogenic T cell activation, suppress B cells from activating and antibodies from producing, and inhibit Akt phosphorylation [32]. SARS-CoV-2: prevents the binding; inhibits the entry; hinders viral genome replication and transcription; interferes with the translation and assembly; prevents Cytokine Storm [32].

Table 1: Antiviral Activity of TriAntiVP.

Bilberry
Overview
Antiseptic, antimicrobial, cardioprotective antibacterial, antifungal, antiallergenic, and antiviral activity [33]
AntiViral
Poliovirus type 1 (PV-1), coxsackievirus B1 (CV-B1), human respiratory syncytial virus A-2 (HRSV-A2), and influenza virus A/H3N2 of Orthomyxoviridae.
Antiviral Targets
inhibits inflammatory gene expression *in vitro* [34,37] preventing Cytokine Storm.

Vitamin D_3
Overview
Direct antimicrobial activities including viruses, Gram-Positive, and Gram-Negative bacteria [47]
AntiViral
Influenza A; SARS-CoV-2; Dengue
Antiviral Targets
Kill the invading pathogens by perturbing their cell membranes [48] and can neutralize endotoxins' biological activities [48], enhances Natural Killer Cell activity [46,54,56,58], and reduces proinflammatory cytokines [51].

Table 2: Antiviral Activity of TriAntiVP.

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