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Review Article

«Proteflazid®» - Antiviral Agent from Ukraine

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Abstract

Aim: To summarize and systematize current knowledge on the pharmacodynamics of PROTEFLAZID®, an original antiviral drug developed from the innovative active pharmaceutical ingredient (API) Proteflazid, focusing on its clinical efficacy, mechanisms of action, and therapeutic significance for viral diseases of various etiologies. Materials and Methods: A systematic review of over 230 clinical and experimental studies, including controlled, randomized, and placebo-controlled trials conducted from 2000 to 2024. The analysis encompassed published articles, clinical guidelines, and regulatory data on the efficacy, safety, and pharmacodynamics of PROTEFLAZID® and its pharmaceutical forms (drops, syrup, suppositories, capsules) in patients of all age groups with RNA and DNA viral infections. Results: PROTEFLAZID® demonstrates a multi-targeted pharmacodynamic profile, exhibiting direct antiviral activity against both RNA and DNA viruses through inhibition of viral-specific enzymes (DNA and RNA polymerases, thymidine kinase, reverse transcriptase, 3CL protease, neuraminidase). The drug has pronounced interferonogenic, immunomodulatory (without inducing refractoriness of the immune system), antioxidant, and apoptosis-modulating effects. Clinical trials involving more than 31,000 patients confirmed the drug's efficacy and safety in preventing and treating viral infections, including influenza, herpesviruses, hepatitis B and C, human papillomavirus, cytomegalovirus, and SARS-CoV-2. PROTEFLAZID® was shown to reduce viral load, normalize immune cell populations, stimulate endogenous interferon production, improve antioxidant defenses, and decrease the risk of complications and mortality. The drug is well-tolerated, non-immunotoxic, and suitable for use in all age groups. Conclusions: The results substantiate the practical value of Proteflazid-based antivirals for effective and safe prophylactic and therapeutic use in viral diseases of diverse etiology.

Keywords

Proteflazid®, RNA & DNA Viruses, Prevention, Treatment, Pharmacodynamics

1. Introduction

In the early 2000s, the range of the antiviral agents was supplemented by the original innovative medicinal product Proteflazid® (developed by SMC "Ecopharm" LTD, Kyiv, Ukraine). Proteflazid® exerts the direct antiviral, interferonogenic, immunomodulating, anti-inflammatory, apoptosis-modulating and anti-oxidant effects, and is of great practical importance in the modern public health practice across different age groups of patients. The studies of the medicinal product involved the evaluation of its efficacy and safety in the various pathologies of viral etiology. Proteflazid is a liquid ethanol extract made of the Deschampsia caespitosa L. and Calamagrotis epigeios L. wild grasses. The medicinal product

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has the original composition containing the flavonoid aglycons (tricine, apigenin, and luteolin). In the following years, based on the drug substance (DS, active pharmaceutical ingredient, API) Proteflazid (hereinafter referred to as Proteflazid), the range of the medicinal products with the following dosage forms were developed: drops, syrup, suppositories, and capsules. In 2018, the site (where the dosage forms based on DS Proteflazid were manufactured with the full cycle) received GMP Certificate.

In 2000–2024, more than 230 clinical studies (controlled, comparative, randomized, placebo-controlled) were conducted; they confirmed the efficacy and safety of the range of medicinal products based on drug substance Proteflazid (hereinafter: medicinal products Proteflazid®, drops; Flavovir®, syrup; Proteflazid®, suppositories, Flavovir®, capsules). More than 31 thousand subjects took part in the clinical studies; among them, more than 21 thousand of patients from the different age, social and other groups received medicinal product Proteflazid for etiotropic treatment of viral diseases caused by RNA and DNA viruses [1, 2]. The study results have been published in many scientific international jurnals and in Ukraine. Based on the accumulated clinical results of using the medicinal products with drug substance Proteflazid in the therapy of diseases caused by the viruses of influenza and ARVI, herpes, human papillomavirus, hepatitises and HIV infection, the Ministry of Health of Ukraine issued 20 guidelines and 28 information letters "On innovations in the healthcare system pertinent to the diseases caused by the viruses of influenza and ARVI, herpes, human papillomavirus, hepatitises and HIV infection". The clinical studies formed the basis for a number of planned research and practical studies conducted by the research institutes of the Academy of Medical Sciences of Ukraine and health care institutions of the Ministry of Health of Ukraine. Some Ph. D. (38) and doctor's (9) theses were defended on this subject [1] (Figure 1).

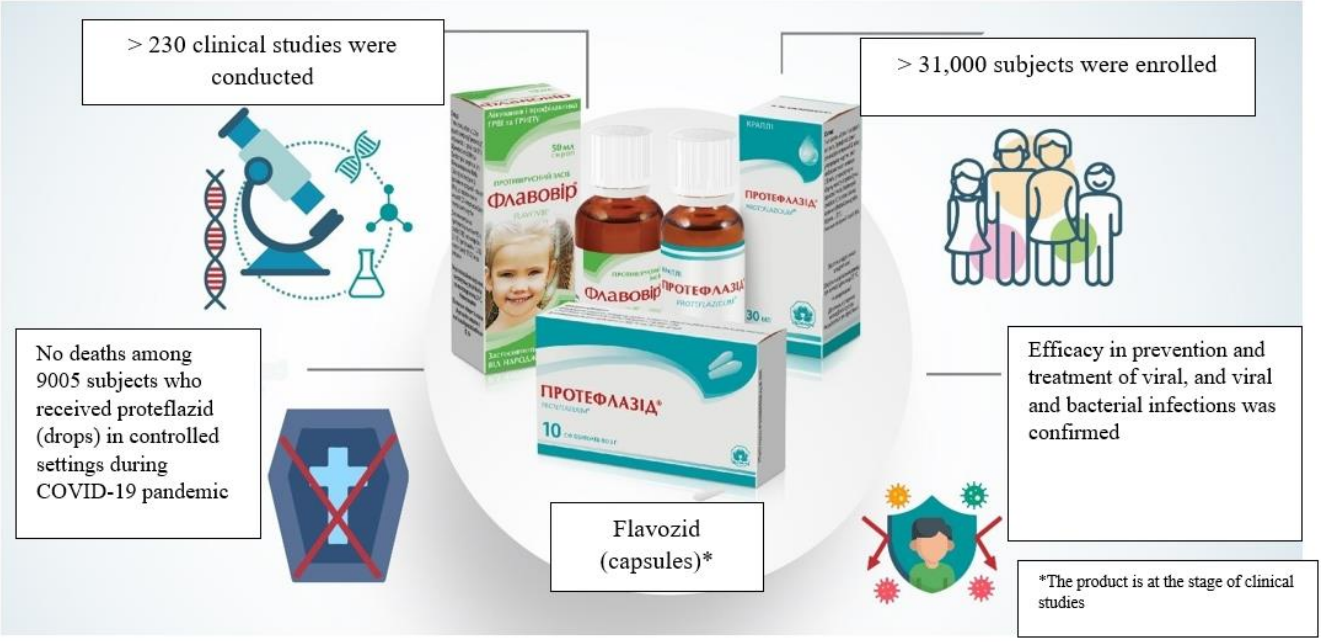

Figure 1. *Clinical studies of dosage forms with drug substance Proteflazid.*

As of today, based on the state registration requirements to the medicinal products in Ukraine, Proteflazid®, drops; Proteflazid®, suppositories; Flavovir® syrup and Proteflazid®, liquid extract (substance) have undergone a complete cycle of the preclinical and clinical studies with the subsequent state authorization (Proteflazid®, liquid extract (substance) was registered in Ukraine in 2017, Marketing Authorization No. UA/16415/01/01 dated May 31, 2022, No. 901, reregistered in Ukraine, the validity period of the Marketing Authorization in Ukraine is unlimited; Proteflazid®, drops was registered in Ukraine in 2002, Marketing Authorization No. UA/4220/01/01 dated September 21, 2020, No. 2143, reregistered in Ukraine, the validity period of the Marketing Authorization in Ukraine is unlimited; Flavovir®, syrup was registered in Ukraine in 2016, Marketing Authorization No. UA/5510/01/01 dated May 25, 2021, No.1032, reregistered in Ukraine, the validity period of the Marketing Authorization in Ukraine is unlimited; Proteflazid®, suppositories was registered in Ukraine in 2015, Marketing Authorization No. UA/4220/01/01 dated September 30, 2020, No. 2220, reregistered in Ukraine, the validity period of the Marketing Authorization in Ukraine is unlimited). The medicinal products with drug substance (API) Proteflazid belong to the following pharmacotherapeutic group: Direct acting antiviral drugs. ATC code: J05A X [1].

It is important to note that in addition to Ukraine, the antiviral product Proteflazid® used in different dosage forms is

being actively registered in other countries. As of 2025, Proteflazid has been already registered in Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Uzbekistan and the Republic of Nigeria.

This article pays special attention to the important aspect of the mechanism of action of the innovative products with the drug substance (API) Proteflazid.

2. Aim

The aim of this paper is to summarize and systematize the current data on the pharmacodynamics of the original antiviral medicinal products developed on the basis of the innovative active pharmaceutical ingredient (drug substance) PROTEFLAZID® focusing on its clinical efficacy, mechanisms of action and therapeutic value in the viral diseases of various etiologies.

3. Materials and Methods

A systematic review of over 230 clinical and experimental studies (including the controlled, randomized, and placebo-controlled trials in 2000-2024) was performed. Published articles, clinical guidelines, and regulatory data pertinent to the efficacy, safety, and pharmacodynamics of drug substance PROTEFLAZID® and its dosage forms (drops, syrup, suppositories, capsules) used in patients of different ages with the diseases caused by viral infections were analyzed.

4. Review and Discussion

4.1. Direct Antiviral Effect

Drug substance Proteflazid reduces the viral load both *in vitro*, and *in vivo* of the following viruses: influenza viruses [3-10]; adenoviruses [11]; enteroviruses [12]; herpesviruses (types I–III) [2, 13-30]; hepatitis C and B viruses [2, 31-40]; Epstein-Barr viruses [41, 42]; human papilloma viruses [15, 43-57]; cytomegaloviruses [58, 59]; HIV [60]; SARS-CoV-2 [5, 42, 61-78] and in the mixed viral and bacterial infections [79-81] (Figure 2).

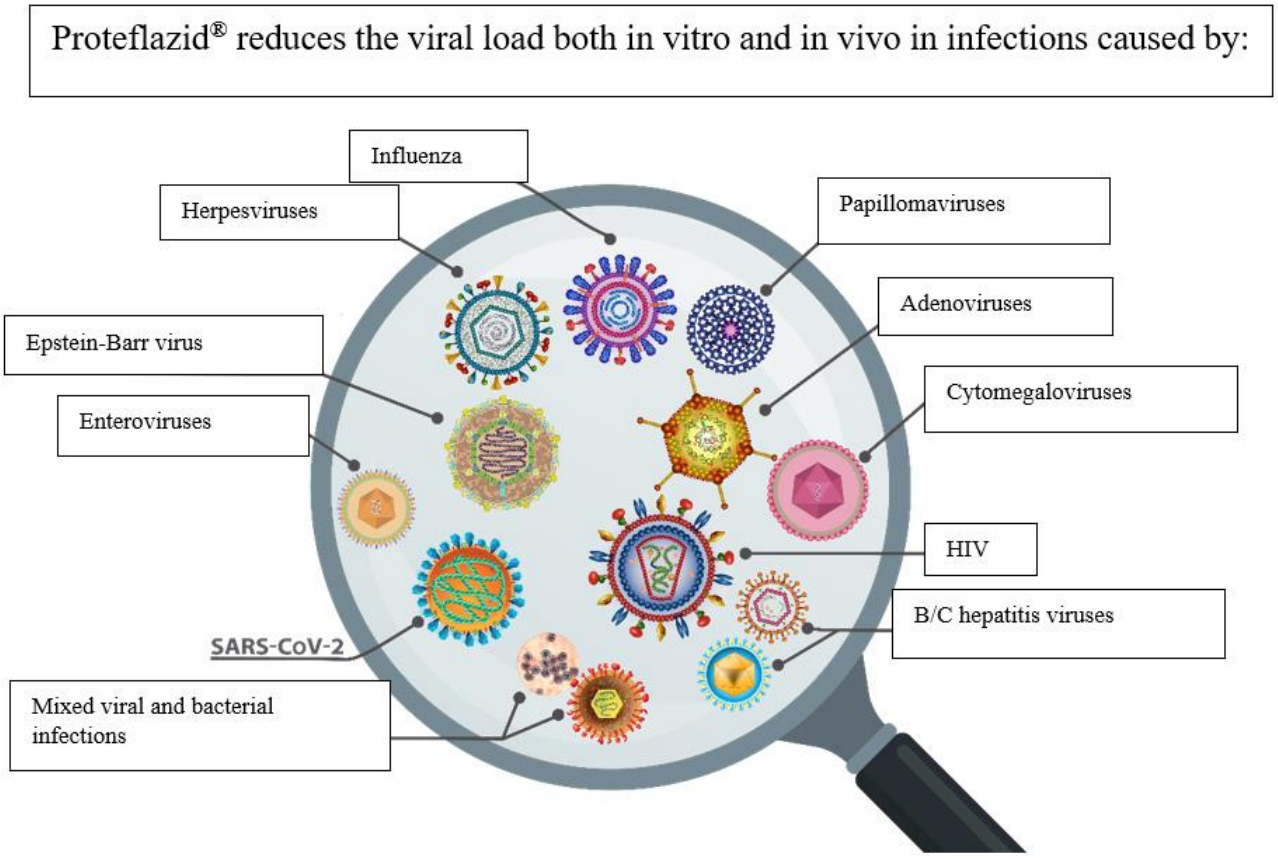

Figure 2. *Proteflazid reduces the viral load both in vitro and in vivo.*

DS Proteflazid decreases the viral load value (of DNA and RNA viruses). It should be noted that the viral load value correlates with the severity of the infectious process: the higher the level of the viral load, the higher the severity of the process. The parameter has the prognostic significance: its increase over time is associated with the significantly increased risk of

disease. The parameter is used to assess the treatment efficacy. The low values of the parameter during therapy are prognostically favorable, the high values are unfavorable. The antiviral effect of medicinal product Proteflazid is associated with the inhibition of DNA and RNA virus replication both *in vitro*, and *in vivo*. It has been proven that the mechanism of the direct antiviral effect involves the inhibition of the virus-specific enzymes — DNA and RNA polymerases, thymidine kinase, reverse transcriptase, 3CL protease, and neuraminidase (Figure 3).

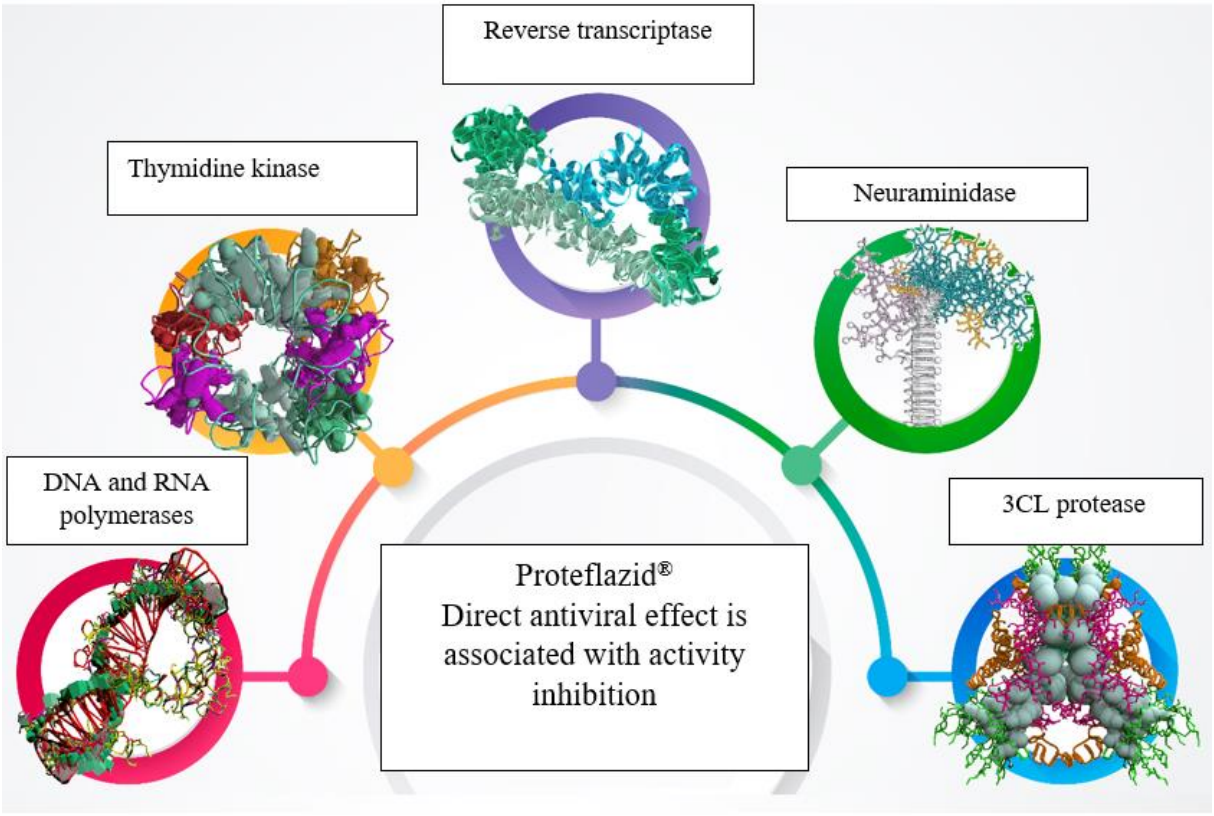

Figure 3. *Mechanism of DS Proteflazid direct antiviral effect on DNA and RNA viruses.*

During the preclinical and clinical studies, the antiviral effect of the medicinal product against DNA and RNA viruses was identified and proven [1, 2, 5].

As for the influenza viruses, the detected property of DS Proteflazid to not only inhibit the neuraminidase activity, but also (unlike other antiviral products of this class recommended for the treatment of influenza) to suppress the intracellular replication of influenza viruses by inhibiting the synthesis of virus-specific enzymes — thymidine kinase and RNA polymerase — is important, i.e. the medicinal product has a poly-target mechanism of the direct antiviral action. Another significant difference between medicinal products with DS Proteflazid and influenza neuraminidase inhibitors (especially in the epidemic periods, as the influenza accounts for only 6% to 10% of ARVI patients in the incidence pattern) is that DS Proteflazid — due to the broad spectrum of the direct antiviral effect — is able to inhibit the replication of not only influenza viruses, but also other RNA and DNA viruses that are in the list of seasonal ARVI [1, 2, 5] including the viruses resistant to the antiviral products with a single antiviral mechanism of action.

DS Proteflazid property to block the replication of RNA and DNA viruses was revealed more than 15 years ago and was used as the basis for the theoretical justification of studying the active substance due to its specific antiviral activity against the coronavirus family, as the scientists around the world are now actively searching for the medicinal products — inhibitors of RNA polymerase and 3CL-like protease of SARS-CoV-2 viruses. It is known that the active targets of the antiviral products with the effects on SARS-CoV-2 coronavirus replication processes may be: RNA polymerase, 3CL-like protease, and transcription factor Nrf2 (Figure 4) [65, 66].

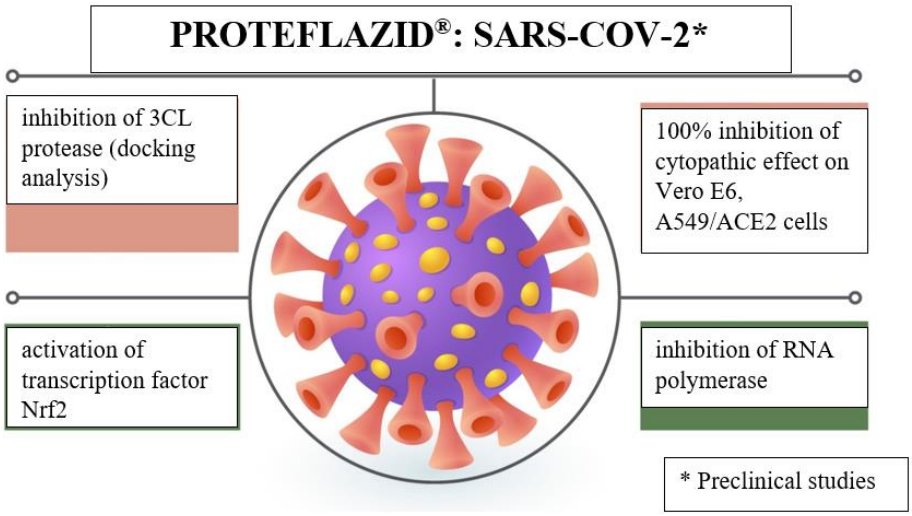

Figure 4. *DS Proteflazid inhibits the synthesis of virus-specific enzymes (3CL protease, RNA polymerase) and activates Nrf2 transcription factor of SARS-CoV-2 viruses.*

At the beginning of 2020, it was demonstrated in the articles of Chinese, Korean and Ukrainian scientists that flavonoids contained in Proteflazid inhibit the activity of 3C-like protease and bind ACE-2 (angiotensin-converting enzyme-2), which acts as a receptor to the coronavirus surface spike glycoprotein facilitating the virus entry into the human cells [61, 64, 65].

In early 2020, the preclinical studies using the molecular docking method demonstrated that Proteflazid was well positioned in the catalytic pocket of 3CL protease of SARS-CoV-2 coronavirus forming the hydrogen bonds with 144 Ser, Gly 143 residues being located between His 163, Asn 142 and Cys 145 catalytic residues, and hydrogen bonds with two catechol hydroxyls with Glu 166 residue indicating the inhibition of 3CL protease activity of SARS-Cov-2 coronavirus. The preclinical studies of Proteflazid revealed that Proteflazid was an inhibitor of RNA and DNA polymerase of influenza viruses and ARVI [64].

Materials of the research and experimental work of specialists from the State Institution "L. V. Hromashevskyi Institute of Epidemiology and Infectious Diseases of the Academy of Medical Sciences of Ukraine" showed that Proteflazid had a high antiviral activity *in vitro* using the model with the transmissible gastroenteritis ("distant relative" of porcine coronavirus) inhibiting the replication of RNA-containing coronavirus (efficacy was confirmed using two cell cultures) — structurally similar to the human coronavirus — by 1,000,000 times or 6 logarithms [64].

The German Helmholtz Centre for Infection Research (Germany) investigated the specific antiviral activity of Proteflazid *in vitro* against human coronavirus CoV-229E. The evaluation of bioluminescence (Dual Luciferase Reporter Gene Assay) demonstrated that Proteflazid significantly inhibited the replication of CoV-229E virus [70].

The Animal Health Research Centre (IRTA-CreSA, Autonomous University of Barcelona, Spain) investigated the specific antiviral activity of Proteflazid against SARS-CoV-2 coronavirus (isolated from 89-year-old patient with COVID-19) *in vitro* using Vero E6 cell culture. Proteflazid demonstrated the high antiviral activity against SARS-CoV-2 [67].

The USA researchers from the laboratory (specializing in SARS/MERS/COVID-19 (P-3) viruses) of the Department of Microbiology and Immunology of Center of Biosecurity and Emerging Diseases (Galveston National Laboratory, University of Texas Medical Branch, Galveston, USA) conducted *in vitro* studies using African green monkey kidney cell cultures (Vero E6) and human pulmonary adenocarcinoma cells with ACE2 receptor (A549/ACE2) and demonstrated that Proteflazid was capable to prevent the virus-induced cytopathic effect caused by SARS-CoV-2 (USA-WA-1/2020 isolate), and ensure 100% antiviral protection against the cell damage caused by SARS-CoV-2 virus [63].

The published research studies confirm that flavonoids, apigenin and luteolin (components of API Proteflazid) activate the transcription factor Nrf2, thereby reducing the expression of angiotensin-converting enzyme (ACE-2, angiotensin-converting enzyme-2) receptors in the human respiratory epithelial cells and prevent the virus entry into epithelial cells blocking SARS-CoV-2 viral replication, and protecting cells from oxidative stress and inflammation, thus reducing the severity of the disease caused by the SARS-CoV-2 virus and, as a result, reducing the probability of the acute respiratory distress syndrome [68, 69, 71, 74, 76-78].

Based on the published data, flavonoid luteolin (one of the components of API Proteflazid) has the broad spectrum of antiviral activity. Luteolin is specifically bound to the surface spike protein of the SARS-CoV-2 coronavirus and inhibits the virus entry into the human cells. Luteolin also exerts the anti-inflammatory effect [73, 75].

In its turn, another flavonoid that is an ingredient of Proteflazid, tricin (the main component) is capable to inhibit the activity of viral enzymes (polymerase and protease) by blocking the replication of RNA and DNA viruses. It has been

shown to effectively reduce the viral load in infections caused by the influenza viruses, herpesviruses, coronaviruses, etc. [78, 82, 83]. Tricin has been shown to reduce the production of pro-inflammatory cytokines helping to control the excessive immune response to the viral infections (e.g., the so-called "cytokine storm") [73]. Tricin stimulates the production of interferons, the natural antiviral proteins that increase the body's resistance to viruses. Tricin has been found to protect the cells from the oxidative stress associated with the viral infections, thus reducing the cell damage [72]. In the preclinical settings, tricine has shown the pronounced antiviral activity in cell cultures inhibiting influenza A virus replication and reducing virus-induced cell apoptosis [82]. The flavonoids, particularly tricin, inhibit the viral attachment and entry into the target cells and reduce the symptom severity in the preclinical models [78]. Tricine has been shown to have a potential inhibitory effect on the 3CLpro protease of SARS-CoV-2 blocking the viral replication at the cellular level [73].

A specific situation with the ARVI treatment has been observed in the recent years, when the pandemic coronavirus — SARS-CoV-2 and its varieties — has spread around the world. From February 2020, prior to WHO statement of pandemic, pharmacological company Ecopharm initiated its own humanitarian action to protect the medical staff in the clinics admitting SARS-CoV-2-infected patients and provided more than 30 thousand vials of medicinal product PROTEFLAZID® (drops) at no cost to more than 140 hospitals involved in providing care to the patients with COVID-19. The volume of charitable assistance and reports on the using the medicinal product PROTEFLAZID® obtained from the healthcare institutions allowed summarizing the experience of the preventive and therapeutic use of medicinal product PROTEFLAZID® directly in COVID-19 patients. The National Academy of Statistics, Accounting and Audit of Ukraine analyzed the reports from the healthcare institutions about the results of using medicinal product PROTEFLAZID®. The reports from the healthcare institutions outlined that the medical staff was in contact with the potential COVID-19 patients and had the high risk of exposure to the coronavirus infection [65, 66]. In total, 8,572 persons administered the medicinal product PROTEFLAZID® for preventive purpose in the specified period; they included 7,444 health care workers and 1,128 patients. The total number of persons who received the medicinal product PROTEFLAZID® for the purpose of treatment was 433 subjects. In total, 9,005 persons (including the medical staff and patients) used the medicinal product PROTEFLAZID® (drops) for the purpose of prevention and treatment. The statistical parameter "Number of fatal cases" among the patients and staff of the healthcare institutions was "0". In general, in comparison with the official data on COVID-19, among the persons who used the medicinal product PROTEFLAZID®: — there were no fatal cases; — proportion of sick medical staff in the healthcare institutions was decreased by 2.2; — proportion of patients with the severe disease was decreased by 3.3; — mean treatment period was decreased by 1.8.

It has been determined in recent years that the mechanism of the direct antiviral action of the medicinal product PROTEFLAZID® used in the acute respiratory viral infection associated with COVID-19 was attributable to: a) inhibition of activity of 3C-like protease that is essentially important for replication of SARS-CoV-2 virus; b) inhibition of RNA polymerase needed for replication of SARS-CoV-2 virus; c) activation of transcription factor Nrf2 that reduces the expression of angiotensin-converting enzyme 2 receptors in the respiratory epithelial cells preventing the virus from entering the lung epithelial cells and suppressing SARS-CoV-2 virus replication thus protecting body cells from the oxidative stress and inflammation, reducing the probability of the acute respiratory distress syndrome. That is, the medicinal product PROTEFLAZID® has a poly-target (multi-target) mechanism of the direct and indirect antiviral effect on SARS-CoV-2 coronavirus and inhibits the pathogenic processes caused by the viral infection (antioxidant, anti-inflammatory, apoptosis-modulating and immunomodulating effects) [65, 66]. Considering the extremely difficult situation with the morbidity and mortality of the country's population caused by the COVID-19 pandemic, SMC "Ecopharm" LTD (Ukraine) conducted the clinical study: "Multicenter, randomized, double-blind study of efficacy and tolerability of FLAVOVIR® (capsules) in patients with the moderate COVID-19 receiving background therapy" in the pandemic conditions and during the war. FLAVOVIR® (capsules) is the innovation of the SMC "Ecopharm" LTD developed as a new dosage form based on the substance derived from DS (API) Proteflazid using the know-how technology. Based on the obtained results, the superior efficacy of the medicinal product FLAVOVIR® (capsules) versus placebo was confirmed secondary to the standard background therapy in the patients with the moderate COVID-19. The results have demonstrated the good therapeutic effect of medicinal product FLAVOVIR® (capsules) in the patients with COVID-19 [62]. Further studies conducted in this field will allow introducing a new effective medicinal product with the direct antiviral effect into the clinical practice of family medicine. This product will play an important role in the fight against such predicted viral threats as "Disease X" [1].

It should be noted that Ukraine was the first country globally whose scientists managed to develop the medicinal product (PROTEFLAZID®) with the direct effect on the human papillomavirus (HPV) including its oncogenic types and prove its efficacy and safety in the treatment of patients with the papillomavirus infection (PVI) and cervical dysplasia (cervical intraepithelial neoplasia, CIN) in the clinical studies [15, 44, 46-51]. Preliminary data of the preclinical studies have shown that PROTEFLAZID® decreases the viral load and normalizes the mitotic activity of the cells transfected with papillomavirus DNA by inhibiting the expression of papillomavirus proteins L1 and E7 concomitantly enhancing the expression of cellular proteins that are the products of the tumor suppressor genes. PROTEFLAZID® inhibits the replication of the

viral DNA, normalizes the mitotic activity of the cells transfected with papillomavirus DNA and enhances the expression of the tumor suppressor proteins (p53, Rb) [54]. The therapeutic effect of the active substance (contained in PROTEFLAZID®) involves the combination of the antiproliferative, proapoptotic and direct antiviral effects indicating the poly-target mechanism of its action. Thus, the Ukrainian scientists and clinicians managed to significantly impact the course of the above mentioned precancer pathology, and, as a consequence, facilitate the prevention of the cervical cancer being one of the most prevailing and dangerous female malignant tumors and that is so important today, in the period of demographic crisis observed both in Ukraine and in the countries of the European and Asian continents [1].

4.2. Immunotropic Effect

Proteflazid normalizes T-lymphocyte [84], T- and B-lymphocyte counts [85]. Blood T- and B-lymphocyte level is a nonspecific parameter indicating that the inflammatory processes are present in the body. The more marked the leukocytosis, the more severe the process. The lymphocyte count decreases as the immune function is suppressed [86] indicating the chronic inflammation [87]. T-lymphocytes reflect the status of the cellular immunity, B-lymphocytes — the humoral immunity. T-lymphocytes (effectors) recognize the antigen, and then, with the help of interleukins, trigger the proliferation of CD4 lymphocytes that recognize the antigens [88]. T-lymphocytes increase the expression of IL-2, IL-4 interleukins [87] and synthesis of interferon-gamma [89]. T-lymphocytes and macrophages are accumulated in the tissue, they find the antigens and destroy them damaging the tissues in which the antigen is located.

Proteflazid increases CD4-lymphocyte counts [90]. The lower CD4-lymphocyte counts, the higher the probability of uncontrolled viral replication [91]. As CD4 T-lymphocyte counts decline, the risk and severity of the opportunistic infections increases [86]. The mechanism involves the modulation of T- and B-lymphocyte functions due to the action of interferons [87].

Proteflazid decreases CD8-lymphocyte counts [92]. CD8-lymphocytes are the cells suppressing the body's immune response. Increased blood CD8 counts indicate the lack of immune response, while the decreased counts are indicative of the hyperresponsive immune system [91]. CD8 levels increase with the viral activity progression [86]. The inflammatory process is associated with the decreased CD4+/CD8+ ratio (immunoregulatory index) and increased relative peripheral blood content of CD8+ cells.

Proteflazid increases the interferon-alfa levels [32, 33]. Usually, the low serum interferon-alpha levels (no antigen stimulation) and high antigen-stimulated leukocyte interferon-alpha and interferon-gamma levels are found in the blood of healthy people [87]. In the acute viral infections, the serum interferon levels are increased, and leukocytes produce a lower interferon response (depletion of interferon synthesis). In the chronic viral infections, even more marked inhibition of interferon production by leukocytes is observed [87]. Interferon inhibits the viral RNA binding with the cellular ribosomes. The most active antiviral effect is observed before infection or at the very beginning of the viral replication [87]. Interferon enhances the function of neutrophil leukocytes, and the phagocytic activity of macrophages, modulates the functions of T- and B-lymphocytes [87], and activates macrophages and NK cells [88].

Proteflazid increases the interferon-gamma levels [3]. The interferon-gamma level is the parameter reflecting the activity degree of the cell-mediated immunity [93]. The reduced interferon production in the infected body means the insufficient protection of the undamaged cells. The interferon-gamma production [87] is enhanced by T-lymphocytes. Interferon-gamma enhances the antibody production, lymphocyte cytotoxicity, macrophage phagocytosis, [88] and initiates the apoptosis [87].

Proteflazid increases the blood NK cell (CD16) counts [94, 95]. NK cells are responsible for the antiviral and antitumor immunity; they destroy the target cells (cells infected with viruses). The decreased CD16 counts lead to the aggravated course of the viral infections. This parameter indirectly reflects the trend towards the increased incidence of the acute respiratory infections [95]. NK cells destroy any cells that have IgG on their surface. NK cells exert the cytotoxic effect by impairing the permeability of the target cells causing their death.

Proteflazid increases IL-2 levels [93, 96]. Interleukin IL-2 is a T-cell growth factor involved in the antitumor, antiviral, and antibacterial responses (causing their antigenic proliferation). The increased lymphocyte levels result in the increased IL-2 expression [87]. IL-2 triggers the growth of cells that are active against microorganisms and viruses.

Proteflazid increases IL-4 levels [93, 96]. Interleukin IL-4 is considered to be a cytokine that tempers the immunoinflammatory responses and impairs the body response to infection. IL-4 is a growth factor for the proliferation of B-lymphocytes [94]. It tempers the immunoinflammatory responses suppressing the expression of IFN-gamma.

Proteflazid decreases interleukin IL-12 levels [97]. IL-12 is a key parameter of enhancing the cell-mediated immune response and initiating the anti-infective protection against viruses. Interleukin prevents the transition of the standard-intensity immune response to the autoimmune process.

Proteflazid increases the total count of macrophages [96]. The macrophage level is the parameter of phagocytic activity reflecting the elimination level of the cells affected by a virus or bacteria. It activates B-lymphocytes. Proteflazid causes the restoration of the functions of the phagocytic component of immunity (increased phagocytic count and percentage of phagocytic cells) [95]. When antigen contacts with a macrophage, it is processed by it, and then presented to T-lympho-

cytes having antigen receptors on their surface [88]. The macrophages actively capture, engulf and digest the damaged cell fragments and toxic products.

Proteflazid regulates the expression level of RIG receptors. The expression level of RIG-I receptors reflects the activity of interferon synthesis. Influenza virus interacts with the RIG-I receptor, induces the decreased RIG-I mRNA response, which in turn leads to the inhibited interferon synthesis [98].

Proteflazid enhances expression of the toll-like receptors — TLR-2, -3, -7, and -9 [99]. The expression level of TLR-2, TLR-3, TLR-7, and TLR-9 reflects the activity of interferon synthesis. TLR signaling pathway is inhibited in the viral infection [99, 100]. TLR expression levels directly correlate with the process severity allowing to consider these receptors as early markers of infection [101]. Increased TLR expression is a key indicator of the acute phase response of innate immunity. TLR is a marker of the foreign ligands entering the body. The products of non-infectious origin (heat shock proteins, uric acid, necrosis and apoptosis products) react with the RNA and DNA fragments [87]. TLR recognizes the pathogen-derived ligands, produces and transmits a signal for the expression of various immune response genes (pro-inflammatory cytokines and interferon-induced genes). They are expressed on the cells of the acute phase response system of the innate immunity — macrophages, neutrophils, monocytes, and B- and T-lymphocytes.

Proteflazid decreases IgM concentration [26, 52]. IgM is produced in response to the acute infection process. IgM indicates the current [102] or recent exposure to a pathogen [86]. Decreased IgM production suggests the reduced antigen load [103]. Interferon activates macrophages and NK cells; then they synthesize IFN, IL-2 and IL-4, as a result of which macrophages and NK cells begin to lyse virus-infected cells [89].

Proteflazid increases the secretory IgA concentration [95]. Secretory IgA (sIgA) indicates the intensity of mucous membrane protection from the pathogenic microorganisms, potential allergens and autoantigens through the local immune mechanisms. The sIgA changes the receptor spatial configuration and prevents pathogen adhesion to it, interferes with the penetration of pathogenic microorganisms in the internal environment of the body. Local blockade of sIgA antigens prevents the immune response with further formation of antibodies.

Proteflazid increases IgG concentration [26]. IgG level is an indicator of toxin-neutralizing, virus-neutralizing, and bactericidal activity. The long-term activity of humoral immunity in the infectious diseases is important for the diagnosis and monitoring of recurrent infections. Detected IgG indicates the current or past infection [102]. It indicates the presence of immune memory to this particular pathogen. The presence of immunoglobulins G is a favorable sign. Persistently low IgG levels may be life-long [102]. Interferon-gamma induces the gene expression in the macrophage genome enhancing the expression of immunoglobulin G receptors. It enhances the immune phagocytosis and antibody-mediated macrophage cytotoxicity. It induces and enhances the production of IL-6, significantly enhances the antimicrobial and anti-inflammatory activity due to the increased production of superoxide radicals by cells. IgG is produced by the activated T-lymphocytes and NK cells.

Based on the results of clinical studies and postmarketing surveillance, it has been demonstrated that as long as medicinal product Proteflazid (regardless of its dosage forms) is administered daily at the age-appropriate doses and dosage regimens, it does not exert the immunotoxic effect and does not cause refractoriness (hyporeactivity) of the immune system. It indicates that Proteflazid has the immunomodulating and interferonogenic properties without developing the refractoriness (hyporeactivity) of the immune system allowing the safety use of the medicinal product both in short-term and long-term therapy in different age groups [1, 23]. It means that even in the long-term or repeated administration of Proteflazid, the patient's immune system does not “get used to” the medicine and does not become less sensitive to its effect. The medicinal product does not deplete or suppress the body's defense mechanisms. Therefore, Proteflazid may be used both for prevention and treatment of the viral diseases (even for a long time) without fear that its efficacy will decrease or undesirable effects for the immune system will appear. In other words, Proteflazid does not lower the patient's ability to fight infections, even in the frequent or long-term administration. It is especially important for the immunocompromised people, children and elderly patients, pregnant women, as well as during the long-term (more than half a year) treatment of diseases caused by herpes viruses, hepatitis and HIV infection. Thus, Proteflazid does not cause damage to the immune system and does not exert toxic (harmful) effects to the immune cells or immune system organs (e.g., bone marrow, lymph nodes, spleen). Even in the long-term or repeated administration, the medicinal product does not cause the complications such as decreased counts of the immune cells, impaired immune response, or increased risk of infections. Therefore, Proteflazid does not suppress, damage or have a toxic effect on the human immune system but it is safe for the body even in the long-term use, in contrast to many other antiviral agents. The medical practitioners should know and remember the properties of medicinal product Proteflazid, as using the medicinal products with the immunotropic effect without studying their property to cause the immune system resistance is a dangerous experiment that can lead either to the desired positive effect of treatment or to the situation that is dangerous to human health and life.

4.3. Antioxidant Effect

Proteflazid increases the activity of superoxide dismutase (SOD) [104]. Proteflazid administration allows avoiding the activation of lipid peroxidation (LPO) [6]. Superoxide dismutase is the antioxidant enzyme protecting the cells from the destructive effects of free radicals [87]. When the cells are

damaged, the activity of prooxidants increases, and the activity of the antioxidant system is significantly decreased. In the immunocompromised patients, the SOD activity level is lowered, making such patients more susceptible to the respiratory infections with the pneumonia development [104]. Low SOD activity level leads to the accumulation of lipid peroxidation products. To decrease the counts of free radicals and toxic lipid peroxidation products by detoxifying free radicals, SOD levels must be increased.

Proteflazid increases the catalase activity [104]. Catalase is the antioxidant enzyme — an indicator of the prevention of free radical damage of cells. When the cells are damaged, the activity of prooxidants increases, and the activity of the antioxidant system decreases significantly. Low levels of catalase activity lead to the accumulation of lipid peroxidation products. Excessive production of LPO products is associated with the cytotoxic, membrane destructive, and immunosuppressive effects. The excessive activation of the peroxidation processes in the influenza intoxication occurs secondary to the decreased AO body defenses, as evidenced by the low activity of SOD and catalase [105]. To lower the free radicals and toxic lipid peroxidation products by destroying and/or inactivating organic and inorganic peroxides, the catalase levels must be increased.

Proteflazid decreases the malondialdehyde levels [106]. The malondialdehyde level is the indirect indicator of the oxidative damage to cellular structures. The increased malondialdehyde level is the early indicator of the metabolic disorders developing during the oxidative destruction of lipids. In addition to the lipids, free radicals damage the DNA structure, which leads to the occurrence and accumulation of mutations [107]. Under physiological conditions, the intensity of lipid peroxidation processes is insignificant. Malondialdehyde is a product of excessive peroxidation.

4.4. Anti-inflammatory and Apoptosis-Modulating Effects

Proteflazid increases the neutrophilic leukocyte counts [108]. Blood neutrophilic leukocyte level is a nonspecific indicator of the acute local or generalized infectious process suppressed by phagocytosis. This parameter reflects the ability to destroy microbes and viruses. The more marked the leukocytosis, the more severe the process. Neutrophils carry the IgG and IgM receptors on their surface; they help the microorganisms being attached to the phagocyte surface.

Proteflazid lowers the ESR [109]. ESR is the indirect sign of the inflammatory or other pathological process course. This parameter indicates the manifestations of the body's general responses to infection (acute phase response). The higher the ESR, the more pronounced the activity degree of the infectious or inflammatory process [102], being a nonspecific indicator. The decreased ESR level is considered to be a marker of response to therapy. The increased ESR is associated with the increased plasma concentration of the coarsely dispersed proteins (globulins) [107].

Proteflazid lowers the alfa globulin levels [1]. The alpha-1 and alpha-2 globulin level is the non-specific indicator of the acute phase of inflammatory processes. Their increased counts reflect the intensity of the stress response and inflammatory processes [91]. Virus-containing cells excessively increase the antibody synthesis leading to hyperglobulinemia [107]. Alpha globulins secreted by the macrophages are able to inactivate the proteolytic enzymes of bacteria [107]. They are capable to engulf the immune peptides such as interleukins, growth factors, and tumor necrosis factor and eliminate them from the blood flow.

Proteflazid lowers the beta globulin levels [36]. The beta globulin level indicates the immune system activation. The level is increased in the inflammation, being a non-specific indicator (index of antibody activity) [86]. Beta globulins are the transport proteins and are part of the complement system associated with IgG. They are involved in the alternative pathway of complement activation (C_3 component of complement). Complement is a stimulator of the activity of monocytes, macrophages, granulocytes, and B-lymphocytes [107].

Proteflazid is the apoptosis modulator; it enhances the effect of apoptosis-inducing substances and activates caspase 9, thereby contributing to the elimination of virus-infected cells and primary prevention of the chronic diseases secondary to the latent viral infections.

The published research studies confirm that flavonoids, apigenin and luteolin (components of API Proteflazid) activate the transcription factor Nrf2, thereby reducing the expression of angiotensin-converting enzyme (ACE-2, angiotensin-converting enzyme-2) receptors in the human respiratory epithelial cells and prevent the virus entry into epithelial cells blocking SARS-CoV-2 virus replication, and protecting cells from oxidative stress and inflammation, thus reducing the severity of the disease caused by the SARS-CoV-2 virus and, as a result, reducing the probability of the acute respiratory distress syndrome [68, 69, 71, 72, 74, 76-78].

**Note: the listed results should be evaluated only in conjunction with the accompanying clinical data, taking into consideration the nosology and process stage of each specific patient.*

4.5. Excerpt from the Prescribing Information (Instructions for Medical Use) of PROTEFLAZID®, Approved by the Ministry of Health of Ukraine

Currently, the following data are contained in the sections “Pharmacological properties. Pharmacodynamics” and “Clinical particulars. Indications” of the Instruction for medical use of medicinal product (PROTEFLAZIDUM®) (APPROVED by Order of the Ministry of Health of Ukraine No. 2143 dated September 21, 2020; Marketing Authorization No. UA/4220/01/01; CHANGES HAVE BEEN IMPLEMENTED by Order of the Ministry of Health of Ukraine No. 2131 dated November 25, 2022) [23].

4.5.1. Pharmacological Properties Pharmacodynamics

Flavonoids contained in the medicinal product are capable to inhibit the replication of DNA and RNA viruses both *in vitro*, and *in vivo*. The antiviral activity of the medicinal product towards herpesviruses, hepatitises, papillomaviruses, HIV infection, influenza and acute respiratory infections has been revealed and proved in the preclinical and clinical studies. It has been proven that the mechanism of the direct antiviral effect involves the inhibition of the virus-specific enzymes — DNA and RNA polymerases, thymidine kinase, reverse transcriptase, 3CL protease and neuraminidase. Proteflazid inhibits the activity of the 3CL protease of SARS-CoV2 coronavirus, which was confirmed by molecular docking and using an assay kit containing 3CL protease labeled with MBP (maltose-binding protein of the SARS-CoV2 coronavirus). The method of dual analysis of the Renilla luciferase reporter gene (reproducing the replication of the seasonal coronavirus CoV-229E) shows that the medicinal product blocks it. In the preclinical *in vitro* studies on monkey cell cultures (Vero E6) and A549/ACE2 human cell cultures, the antiviral activity against the pandemic human coronavirus SARS-CoV-2 was demonstrated (with the significant inhibition of virus replication).

The medicinal product has immunotropic properties. It protects the mucous membranes normalizing the local immunity parameters (lactoferrin, secretory immunoglobulin A, lysozyme and C_3 component of the complement). The medicinal product has found to be the inductor of synthesis of endogenous α- and γ-interferons to physiologically active level increasing the non-specific body resistance to the viral and bacterial infections. The clinical studies have demonstrated that if the product is administered daily at the age-appropriate doses and dosage regimens, it does not exert the immunotoxic effect and does not cause refractoriness (hyporeactivity) of the immune system: no inhibition of the synthesis of α- and γ- interferons is observed allowing the long-term administration of the medicinal product.

The medicinal product exerts the antioxidant activity, inhibits the free radical processes, thereby preventing the accumulation of lipid peroxidation products and enhancing the antioxidant status of cells, decreases the intoxication, promotes the body recovery after the infection and adaptation to the adverse environmental factors. The medicinal product is the apoptosis modulator; it enhances the effect of apoptosis-inducing substances and activates caspase 9, thereby contributing to the elimination of virus-infected cells and primary prevention of the chronic diseases secondary to the latent viral infections. The medicinal product prevents the disease recurrences and prolongs the remission periods.

4.5.2. Clinical Particulars Indications

Treatment and prevention of recurrences caused by: - herpes simplex virus, type 1 and 2; - herpes zoster and chicken pox viruses, type 3; - herpesvirus, type 4 (Epstein-Barr virus), acute and chronic active forms; - herpesvirus, type 5 (cytomegalovirus).

Treatment and prevention of influenza and other ARVI (including the ones caused by pandemic influenza strains). As part of the combination therapy of: - hepatitis B and C; - viral, bacterial, fungal infections and their associations (chlamydia, mycoplasma, ureaplasma, etc.); - HIV infection and AIDS. Etiotropic therapy of the mild and moderate cervical dysplasia (CIN1 and CIN2) caused by papillomavirus infection including the oncogenic strains. As part of the combination therapy of other forms of diseases caused by papillomavirus infection including the oncogenic strains" [23].

5. Research and Practical Achievements

Based on the accumulated clinical results of using products with the drug substance Proteflazid in the therapy of diseases caused by the viruses of influenza and ARVI, herpes, human papillomavirus, hepatitises and HIV infection, the Ministry of Health of Ukraine issued 20 guidelines and 28 information letters "On innovations in the healthcare system pertinent to the diseases caused by the viruses of influenza and ARVI, herpes, human papillomavirus, hepatitises and HIV infection". The clinical studies formed the basis for a number of planned research and practical studies conducted by the research institutes of the Academy of Medical Sciences of Ukraine and health care institutions of the Ministry of Health of Ukraine. Some Ph. D. (38) and doctor's (9) theses were defended on this subject [1].

6. International Projects

On February 18, 2019, the project of SMC "Ecopharm" LTD — "*Innovative direct-action anti-HPV agent for cervical cancer prevention*" was honored by the SEAL OF EXCELLENCE certificate from the European Commission; on October 9, 2019, another project of SMC "Ecopharm" LTD — "*Innovative natural direct-action antiviral agent for ARI treatment*" was also honored by the SEAL OF EXCELLENCE certificate from the European Commission. Seal of Excellence is a quality label that Europeans award to the scientists for their project proposals submitted for funding from Horizon 2020, the EU Research and Innovation Framework Program. The European Commission operates one of the most comprehensive assessment systems in the world using the international panels of independent experts and scores the proposals on the defined project criteria: excellence, impact, quality and efficiency of implementation. Awarding SEAL OF EXCELLENCE certificates indicates that projects "*Innovative direct-action anti-HPV agent for cervical cancer prevention*" and "*Innovative natural direct-action antiviral agent for ARI treatment*" submitted by SMC "Ecopharm" LTD were scored by the international panel of independent experts as the "high-quality project proposal in the highly competitive evaluation

process" and passed the stringent Horizon 2020 assessment thresholds for the 3 award criteria (excellence, impact, quality and efficiency of implementation) and, thus, the above-mentioned topics are extremely relevant for the international community.

7. Conclusions

The antiviral medicinal products developed on the basis of the original innovative drug substance Proteflazid exert the direct antiviral, interferonogenic, immunomodulatory (they do not cause immune system refractoriness), antioxidant, anti-inflammatory and apoptosis-modulating effects, that are important for the practical clinical use for the purpose of their effective and safe preventive and therapeutic administration in the patients of all age groups with the various pathologies of viral etiology. Medicinal products containing Proteflazid have the poly-target mechanism of the direct antiviral action; in addition, due to the broad spectrum of the direct antiviral effect, these products are capable to inhibit the replication of not only influenza viruses, but also other RNA and DNA viruses, in contrast to other antiviral agents with the single-target activity, which is especially important during the period of seasonal AVRIs. The therapeutic effect of the flavonoids contained in medicinal product PROTEFLAZID® is achieved due to the combination of the antiproliferative, proapoptotic and direct antiviral effect indicating the poly-target mechanism of its action also in papillomavirus and mixed viral and bacterial infections in gynecological diseases and in viral diseases of other etiology. The poly-target mechanism of the activity of drug substance Proteflazid ensures the protection of the medicinal product from viral microbiota resistance to the drug substance Proteflazid and medicinal products based on this DS.

Abbreviations

API	Active Pharmaceutical Ingredient
RNA	Ribonucleic Acid
DNA	Deoxyribonucleic Acid
3CL-protease	3-Chymotrypsin-Like Protease (Main Protease, Mpro)
DS	Drug Substance
HIV	Human Immunodeficiency Virus
ARVI	Acute Respiratory Viral Infection
CoV-229E	Human Coronavirus 229E
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
IRTA-CReSA	Institute for Research and Technology in Agrifood - Centre De Recerca En Sanitat Animal (Animal Health Research Center, Spain)
ACE2	Angiotensin-Converting Enzyme 2
PVI	Papillomavirus Infection
HPV	Human Papillomavirus
CD	Cluster of Differentiation
NK	Natural Killer (cells)
IL	Interleukin
TLR	Toll-Like Receptor
IgA	Immunoglobulin A
sIgA	Secretory Immunoglobulin A
IgG	Immunoglobulin G
SOD	Superoxide Dismutase
LPO	Lipid Peroxidation
ESR	Erythrocyte Sedimentation Rate

Author Contributions

Oleksandr Yosypovych Hrynevych: Conceptualization, Data curation, Methodology, Resources, Software, Writing – original draft

Conflicts of Interest

The author declares that there is no conflict of interest.

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