Novel non-covalent ivermectin complex Didenectin is revolutionizing healthcare.

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ABSTRACT

COVID-19 pandemic has accelerated scientific knowledge and led to groundbreaking advancements in virology, and it has also given rise development of new viruses based on the coronavirus both in governmental and private laboratories all over the world. Laboratory accidents, no matter how well-controlled, can happen. We need to explore a development of an effective treatment that can mitigate the potential misuse of the coronavirus as a foundation for new viruses.

In this article, we introduce a revolutionary breakthrough in coronavirus treatment, new ivermectin-based complex Didenectin (antiviral ivermectin), which is proved to reduce virus load to 100 times during 24h, leading to revolutionary rapid recovery of SARS-CoV-2 patients and Dengue patients within a record 24-hour timeframe.

The introduction of new non-covalent complex of ivermectin is changing the game in the healthcare industry. A novel non-covalent ivermectin-polymer complex Didenectin, already showed remarkable results on SARS-CoV-2 as well as on Dengue, a condition currently lacking any specific treatment. The complex should also be effective for the treatment of other viral infections that have shown in vitro sensitivity to ivermectin such as Chikungunya, Zika, Yellow fever, West Nile, avian influenza A (H7N7), HIV-1, Japanese encephalitis, tick-borne encephalitis, Epstein-Barr and others.

Ivermectin, a widely recognized anti-parasitic medication, exhibited remarkable efficacy in reducing viral load of SARS-CoV-2 by 93% and more within a single day under in vitro conditions, as demonstrated by Caly et al. However, translating these results to in vivo human studies was hindered by the substantial toxicity of ivermectin, preventing the achievement of the necessary IC_{50} 2.4 μM and IC_{90} 5 μM concentration of ivermectin in body tissues. The advent of the innovative Didenectin allowed to achieve a notable 3.4-fold reduction in oral toxicity and a remarkable 20-fold increase in solubility when compared to standard ivermectin. This led to the achievement of necessary IC_{50} 2.4 μM and IC_{90} 5 μM concentration of ivermectin and comparable reduction in viral load in vivo as previously demonstrated in vitro by Caly et al.

Didenectin's rapid and effective action demonstrates its potential not only for SARS-CoV-2 but potentially for Dengue as well. The first-ever cure of a Dengue patient within a 24-hour timeframe using Didenectin represents a monumental achievement in the field of antiviral research.

This article delves into the complex's mechanism of action, pre-clinical results, as well as a detailed description of the method for obtaining the ivermectin-polymer complex Didenectin, along with the complete formula and table of dosages.

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The newly developed ivermectin-polymer complex, known as Didenectin, is derived from an innovative solid dispersion of ivermectin formed through the novel process of mechanochemical activation. This complex combines with arabinogalactan polymer to create a non-covalent interaction. The ivermectin-polymer complex Didenectin, due to its modified molecular structure, exhibits altered properties, including a 20-fold increase in solubility, increased bioavailability, enhanced permeability, and, simultaneously, a 3.4-fold reduction in oral toxicity compare to ordinary ivermectin. The substantial changes in drug parameters compared to the base compound result in a qualitatively new treatment outcome and results in a significant 100 times reduction in the viral load within the initial 24-hour period. Instead of merely improving treatment efficacy indicators, such as ventilation, ICU admissions, hospitalization, and recovery, the treatment led to the complete recovery of patients in the shortest time possible. The treatment duration for the infection is reduced to just 1 day at a single dose of more than 600-700 μg/kg (according to pure IVM).

As ivermectin is under investigation as an anticancer agent, Didenectin emerges as a promising candidate for cancer treatment due to its low toxicity.

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1. Introduction

In March 2020, Australian researchers (L. Caly et al.) demonstrated that ivermectin, a drug used for decades to combat parasitic infections, had antiviral activity against SARS-CoV-2 in vitro in Vero cell cultures, virtually reducing the viral load to zero in 48 h [1]. Caly et al. bathed Vero-hSLAM cells with ivermectin at a concentration of 5μM from 2 hours post-infection SARS-CoV-2 isolate Australia/VIC01/2020 until the conclusion of the experiment. SARS-CoV-2 RNA was determined by RT-PCR at Days 0–3 in both supernatant and cell pellet experiments. The authors noted 93–99.8% reduction in viral RNA for ivermectin versus DMSO control at 24h in supernatant (released virions) and cell associated viral RNA (total virus) respectively. They also describe by 48 hours a ~5000-fold reduction of viral RNA and maintenance of effect at 72 hours. Additional experiments were conducted with serial dilutions of ivermectin to establish the concentration-response profile, and the authors describe ivermectin as a potent inhibitor of SARS-CoV-2, with an IC_{50} determined to be approximately ~2.4μM, and IC_{90} ~5 μM under these conditions. The experiment of Caly et al. showed that the degree of inhibition of virus replication by ivermectin depends directly on the concentration of ivermectin in the body cells. Once the threshold concentration (IC_{10} ~ 1μM) of ivermectin in the cells is reached, each subsequent increase in the concentration of ivermectin in the tissues of the body increases the inhibition.

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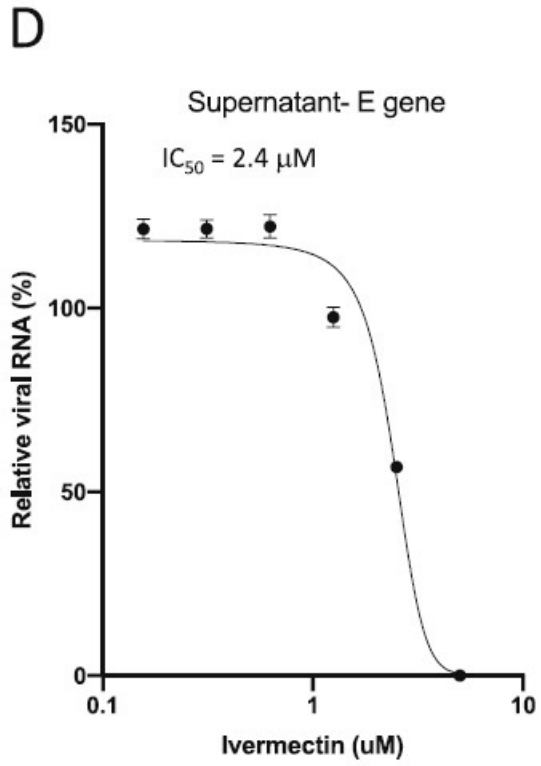

Fig. 1. Ivermectin is a potent inhibitor of the SARS-CoV-2 clinical isolate Australia/VIC01/2020 [1].

The Caly et al. experiment led to a significant number of clinical trials evaluating the effectiveness of ivermectin (in its standard tablet form, approved for the treatment of parasitic infections) against SARS-CoV-2.

However, a plasma concentration of ivermectin compatible with the IC_{50} (half maximal inhibitory concentration) found in vitro ~2.4µM (equivalent to 2101 ng/mL) is far from being achievable with the usual doses of 200–400 µg/kg (0.087–0.258µM equivalent to 36–84 ng/mL) [3, 4, 6]. Even a high dose of the standard tablet form of ivermectin of 600 µg/kg/day during 5 days has been shown to produce a lung C_{max} of 0.46 µM [5] which is much less than its in vitro IC_{50} 2.4 µM and IC_{90} 5 µM and a correspondingly very low degree of viral load reduction [5]. These relatively high doses of the standard tablet form of ivermectin do not provide the concentration of ivermectin in body tissues necessary to effectively inhibit viral replication [3, 4]. All current studies of ivermectin are limited to doses for which the C_{max} in the lungs is less than IC_{10} ~1µM. Given this, the standard tablet form of ivermectin has demonstrated clinical and virological efficacy against COVID-19 that is lower than anticipated [5, 22].

Therefore, there is an efficacy gap between in vitro studies and clinical trials requires a drug delivery system with which to achieve the in vitro levels defined by L.Caly et al.

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2. Solution to Problem

A calculation based on the pharmacokinetic data available for ivermectin dosage-concentration in plasma [3, 4, 5, 6] shows that: 1) there is a nearly linear dose-plasma concentration relationship (R^2=0.94) and 2) that simply increasing the dosage of ivermectin cannot solve the problem of achieving in vitro defined levels because the calculated (by linear regression) dosage of the standard form of ivermectin required to reach these levels is 4630 µg/kg (IC_{50}) to 9683 µg/kg (IC_{90}) respectively and is 4.8-2.3 times greater than the maximum dose studied which has no-observed-adverse-effect level [6] and only 3-1.5 times less than the dose which induces coma in patients [7]. Given that the median lethal doses (LD_{50}) of ivermectin were reported 11.6 mg/kg (oral) in male mice [9] when converted to HEDa [17] gives LD_{50} for humans of 940 µg/kg. It is clear that conventional ivermectin is not capable of acting as a drug in the treatment of COVID-19, Dengue fever and other viral infections that have shown in vitro sensitivity to ivermectin [12, 13].

Table 1. The maximum concentration (C_{max}) in plasma and lung following oral administration of Ivermectin (standard tablet) varies with the dose.*

IVM dose, µg/kg/day[1]	C_{max}in plasma, µM	C_{max} in lung, µM [2]	In vitro IC	Ref.	C_{max}in plasma, ng/mL; IVM dose, mg; comment
200	**0.041**	0.109		[3]	36 ng/ml
200	**0.032**	0.087		[4]	single dose
200	**0.033**	0.088		[4]	weekly
400	**0.096**	0.258		[6]	84.8 ng/ml; 30 mg
600	**0.172**	0.460		[5]	151 ng/ml
600	**0.135**	0.362		[5]	119 ng/ml
800	**0.169**	0.451		[4]	60 mg; every 72 h
800	**0.188**	0.503		[6]	165.2 ng/ml; 60 mg
1200	**0.180**	0.482		[6]	158.1 ng/ml; 90 mg
1600	**0.329**	0.878		[3]	288 ng/ml; 120 mg
1600	**0.307**	0.820		[4]	120 mg
1600	**0.313**	0.836		[4]	120 mg; weekly
1600	**0.282**	0.753		[6]	247.8 ng/ml; 120 mg
1909†	0.374	~1.0	EC_{10} SARS-CoV-2	[1]	
2000	0.391†	1.046	Maximum single dose‡	[6]	
3658†	0.711	1.9	EC_{50} CHIK	[13]	
4436†	0.86	2.3	EC_{50} DENV1	[13]	
4630†	0.9	2.4	EC_{50} SARS-CoV-2	[1]	
9683†	1.87	5.0	EC_{90} SARS-CoV-2	[1]	

* - Doses and concentrations highlighted in bold were used to construct a dose-C_{max} linear regression.
† -Theoretical calculated doses estimated based on linear regression.
[1]- The ingested amount (in µg/kg/day) was derived from an estimated body weight of 75 kg for patients with unknown body weight.
[2]- Calculated by plasma-lung ratio 2.67 [2].
‡ -Maximum single dose have been used in a trial in healthy volunteers without clinically significant safety issues [6].

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Thus, our team faced the task of finding a way to achieve ivermectin tissue concentrations equal to the IC_{50} determined in in vitro studies by Caly et al., taking into account a plasma-lung ratio of 2.67 [2], while considering oral toxicity and cytotoxicity as limiting factors.

In our group, we utilize independent artificial intelligence systems to support decision-making in drug development. A special system was used that involves collaboration between humans and special AI systems. We employed our company's developed Intellectual Drug Repurposing™ (IDR) approach: Intellectual Drug Repurposing involves a systematic exploration of existing drugs to identify new therapeutic indications beyond their originally intended use. IDR goes beyond traditional repurposing by integrating the improvement and optimization of these drugs to maximize their efficacy, safety, and patient outcomes. By leveraging the wealth of knowledge accumulated by special AI system, Artificial Intellect AllAI™, on approved and investigational drugs, IDR capitalizes on the existing data, clinical experience, and safety profiles to accelerate the process of identifying new applications. As result of usage of IDR approach, we developed a novel non-covalent ivermectin-polymer complex named Didenectin.

During our work within the IDR approach, computer analysis revealed that the primary issue with ivermectin is 1) its low water solubility (~ 4 mg/l), resulting in poor bioavailability due to inadequate absorption of ivermectin in the gastrointestinal tract.

Therefore, to achieve the desired concentration of ivermectin in the plasma, it was necessary to develop a method for enhancing the bioavailability of ivermectin. An analysis revealed several approaches to improve the bioavailability of this drug. Among these, a method for creating a solid dispersion (specifically, a solid-phase polymer-ivermectin inclusion complex) was chosen for evaluation. This solid dispersion was subsequently dissolved in an adequate volume of water, resulting in a solution of a non-covalent ivermectin-polymer complex (solubilized non-covalent inclusion complex of ivermectin with a polymer). This method proved to be the most successful.

Solid dispersion is a formulation strategy aimed at improving the solubility and dissolution rate of poorly water-soluble drugs by dispersing them within a solid carrier matrix [27, 28, 29]. This technology offers several advantages, including increased drug solubility, improved bioavailability, and enhanced therapeutic efficacy. In solid dispersion, the drug is intimately mixed with the carrier material, forming a single-phase solid system matrix [27, 28, 29].

Solid dispersion can be created using various methods, such as hot melt extrusion, spray drying, or solvent evaporation [28, 29]. Among the various methods used to prepare solid dispersions, solid-phase mechanochemical technology stands out as a versatile and innovative approach [30].

Mechanochemical synthesized solid dispersion refer to drug-carrier systems or drug-excipient mixtures in which the mechanical force, such as grinding, milling, solid-phase melting or other mechanical processes, is applied to create an intimate and uniform mixture of the drug and the carrier (including solid-phase inclusion complex)[30]. The mechanical force disrupts the crystalline structure of the drug and promotes its dispersion or fusion within the carrier material in an amorphous or disordered form [30]. By promoting rapid dissolution and increased solubility, mechanochemical synthesized solid dispersion can improve the bioavailability of poorly water-soluble drugs. One of the most promising

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applications of mechanochemical activation is in combination with polymers, which are commonly used as carriers in solid dispersions.

In the course of the work, the task was to select a polymer, the complex of which with ivermectin would provide:

a) Reduced toxicity;
b) Increased bioavailability;
c) Enhanced solubility;
d) Improved permeability;
e) Form a non-viscous solution, as the most commonly used polymers tend to form viscous solutions after dissolution in water, which delays the release of the drug from their matrix. Moreover, these polymers are metabolized in the gastrointestinal tract and release the drug primarily in the colon (Sinh V. R. et al., 2001).

Our analysis using our artificial intelligence systems showed that the following polymers would be the best choice - arabinogalactan, pectin, laminarin, polyvinylpyrrolidone and some others.

3. Methods

When treated by the solid dispersion method, ivermectin acquires new molecular properties that are not identical to the pharmaceutical composition, namely modified pharmacokinetic parameters, different system bioavailability, in vivo permeability, reduced by 3.4 times the toxicity, increased reduction of viral load (more than 100 times in first 24 hours, which exceeds the reduction of viral load for the same doses of conventional ivermectin), the treatment time of the infection is reduced to 1 days at doses of more than 600 μg/kg of Didenectinat a single dose.

To manufacture the ivermectin-polymer complex Didenectin, we used the following approach: ivermectin and the polymer are mixed in a ratio ranging from 1:5 to 1:50 or more and processed in a ball mill for 4-5 hours. The resulting powder is expected to be storable for several months.

The preferred polymer is arabinogalactan. If it is not available, apple pectin or polyvinylpyrrolidone can be used, but the effectiveness may be slightly lower.

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Table 2. Table of Dosages per Patient for the Non-Covalent Ivermectin-Arabinogalactan Complex 1:20

	dose 600 µg/kg		dose700 µg/kg		dose800 µg/kg		dose900 µg/kg	
patient weight, kg	weight of ivermectin, mg	weight of arabinogalactan, mg	weight of ivermectin, mg	weight of arabinogalactan, mg	weight of ivermectin, mg	weight of arabinogalactan, mg	weight of ivermectin, mg	weight of arabinogal actan, mg
60	36	720	42	840	48	960	54	1080
65	39	780	45.5	910	52	1040	58.5	1170
70	42	840	49	980	56	1120	63	1260
75	45	900	52.5	1050	60	1200	67.5	1350
80	48	960	56	1120	64	1280	72	1440
85	51	1020	59.5	1190	68	1360	76.5	1530
90	54	1080	63	1260	72	1440	81	1620

Thus, to prepare the complex, it is necessary to calculate the weights according to Table 2, place the weights along with steel balls with a diameter of 12-15 mm and a mass of 500-800 g in the ball mill, set the speed to 70 revolutions per minute, and process the mixture for 5 hours. The total mass of the processed mixture of ivermectin with the polymer should not be less than 10-20 grams and can reach several hundred grams.

For patient intake, the ivermectin-polymer complex Didenectin should be dissolved or suspended in a sufficiently large volume of water (for example, 300 ml) and used immediately after dissolution, as solutions or suspensions undergo degradation due to a strong non-equilibrium state.

The effectiveness of the complex is easily detectable and demonstrable through Real-Time qRT-PCR (Real-Time Quantitative Reverse Transcription PCR) testing, allowing for the instrumental measurement and reliable observation of the reduction in viral load in patients.

4. Research

Toxicity: Acute Oral Toxicity in Mice and Rats

According to prior research [23], the acute oral toxicity was studied by administering the ivermectin complex and pure ivermectin substance in elevated doses to white mice and rats weighing 18 g and 160-180 g, respectively. Each dose was given to 10 mice and 6 rats. The drug was administered once via a stomach tube at doses ranging from 40 to 350 mg/kg (40,000 - 350,000 µg/kg) of Ivermectin. The animals were observed for 14 days, monitoring their general clinical condition, behavior, possible mortality, as well as signs of intoxication (motor activity, condition of eye membranes, fecal color and consistency, food consumption, changes in body weight). Body weight of experimental animals was recorded before and after the experiment on days 3, 7, 9, and 14.

Upon administering the non-covalent ivermectin complex and ivermectin substance to the groups of mice (n = 10) at doses of 200 and 40 mg/kg, respectively, and to rats (n = 6) at doses of 225 and 40 mg/kg, no signs of intoxication were observed. The animals

dynamically gained body weight, and no pathological anatomical changes in internal organs were noted during necropsy on the 14th day.

With an increase in the administered doses to mice and rats, there was a correlation between the number of deceased animals and the dose magnitude. At higher doses of the non-covalent ivermectin complex (ranging from 250 to 400 mg/kg) and the substance (from 50 to 220 mg/kg), animal mortality occurred on days 1, 3, 5, and 12. Before death, the animals displayed signs of depression, lying down with their noses buried in bedding, trembling, and brownish nasal discharges mixed with blood. Upon necropsy of the deceased animals, dark brown exudates mixed with blood were found in the lungs and abdominal cavity. The liver was enlarged and of a dark brown color, with dark fluid exuding upon incision. The spleen was reduced in size, appearing black externally and internally. The kidneys were enlarged, light in color, and contained a white dense mass upon incision. The intestines contained a small amount of food material and exhibited distension. It is likely that the death of animals at elevated doses resulted from hepatorenal and subsequent asphyxia toxicity. The intoxication pattern was comparable between mice and rats, and a correlation between the number of deceased individuals and the administered dose was established. The toxicity of the non-covalent ivermectin complex was 1.8-3.4 times lower than that of the ivermectin substance. The LD_{50} of the ivermectin substance for mice was 82.0 mg/kg and for rats, 165.0 mg/kg. For the non-covalent ivermectin complex, the LD_{50} was 280.0 mg/kg for mice and 298.0 mg/kg for rats (equivalent to 14,500 and 14,598 mg/kg of the drug, respectively).

Table3. Results of Acute Oral Toxicity Study of the Non-Covalent Complex

Mice		Rats	
Dose, µg/kg, (according to pure IVM)	Alive/dead	Dose, µg/kg, (according to pure IVM)	Alive/dead
200,000	10/0	225,000	6/0
250,000	7/3	250,000	5/1
300,000	4/6	275,000	4/2
350,000	1/9	300,000	3/3
400,000	0/10	350,000	1/5

Table4. $LD_{0\text{-}100}$values

Species	LD_0 (mg/kg) (according to pure IVM)	LD_{16}(mg/kg) (according to pure IVM)	LD_{50} (mg/kg) (according to pure IVM)	LD_{84} (mg/kg) (according to pure IVM)	LD_{100}(mg/kg) (according to pure IVM)
Mice	200	230	280	370	400
Rats	225	260	298	320	400

The results of the acute oral toxicity study of the non-covalent ivermectin complex revealed an LD_{50} of 280.0 mg/kg for mice (equivalent to 14,500 mg/kg of the drug) and 298.0 mg/kg for rats (equivalent to 14,598 mg/kg of the drug).

Toxicity assessment: Subchronic toxicity test (rats)

According to prior research [24], 20 non-pedigree white rats weighing 180 g each were selected for the experiment and divided into experimental and control groups, each comprising 10 animals. To determine the cumulative coefficient, a method based on the recording of animal mortality upon repeated administration of the drug was employed, known as the subchronic toxicity test. In the experimental group, the drug was orally administered for the first four days at a dose of 35.5 mg/kg, equivalent to 1/10 of the previously established LD_{50} (298.0 mg/kg). Subsequently, the dose was increased by 1.5 times every four days. The control group of rats received 2 ml of water. The experiment was conducted over a 28-day period. Throughout the experiment, continuous monitoring of the animals was performed, considering their condition and activity levels. Additionally, the following parameters were assessed: the general state of the animals (agitation, depression), the nature and degree of activity, coordination of movements, response to painful stimuli, the presence of tremors, seizures, paresis, paralysis, eye and nasal discharge, urinary tract changes, alterations in skin color, changes in body weight, and appetite.

To determine the cumulative coefficient, a method based on recording animal mortality upon repeated drug administration was used, referred to as the subchronic toxicity test. The study of the cumulative properties of the ivermectin complex revealed that 50% of the animals succumbed on the 22nd day of the experiment. The total dose of the administered drug over this period amounted to 1802.3 mg/kg (Table 5).

Table 5. Cumulative Properties of the Ivermectin Complex

Dayofexperiment	Dailydose, mg/kg	Totaldose, mg/kg	Dead /Alive	
			Experiment	Control
1-4	29.8	119.2	0/10	0/10
5-8	44.7	178.8	0/10	0/10
9-12	67.1	268.2	1/9	0/10
13-16	100.7	402.6	2/8	0/10
17-20	151.1	302.1	4/6	0/10
21-22	265.7	531.4	6/4	0/10
Totalfor 22 days		**1802.3**	**$Coeff_{cum}$ = 1802.3 : 298 = 6.05**	

The study of the cumulative properties of the non-covalent ivermectin complex resulted in the determination of a cumulative coefficient, which equaled 6.05. The non-covalent ivermectin complex falls within the category of substances exhibiting weak cumulative properties.

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Toxicity: Impact of Non-Covalent Ivermectin Complex on the Clinical Condition of Horses

According to prior research [25], the influence of the non-covalent ivermectin complex on the clinical condition of horses was examined. Horses were divided into two experimental groups and one control group, with each group consisting of 5 animals. In the first group, the non-covalent ivermectin complex was administered at a dose of 0.6 mg/kg, while in the second group, it was administered at a dose of 1.0 mg/kg, based on body weight. The drug was administered individually, mixed with feed.

Body temperature was measured using a non-contact thermometer, and pulse and respiration rates were recorded for 1 minute. Urine samples from the horses were analyzed on days 1, 7, and 14 after drug administration, assessing color, transparency, and consistency. Universal indicator paper was used to determine pH, protein, glucose, ketones, nitrites, bilirubin, and urobilinogen.

Blood samples were collected in the morning from the jugular vein of the horses on days 1, 7, and 14 following drug administration. Hematological and biochemical parameters were analyzed using automated analyzers.

Clinical signs in horses (body temperature, pulse, and respiration) after the administration of the non-covalent ivermectin complex at doses of 600 and 1000 μg/kg on days 1, 7, and 14 did not differ from the control group's animal parameters.

Analysis of the horses' urine showed a slight increase in ketone bodies on the first day (up to 5/52) as opposed to the control animals (1.5/16). On days 7 and 14, all indicators were within the normal range.

The non-covalent ivermectin complex did not have a negative impact on hematological parameters; they remained within the normal range.

When studying the effect of the non-covalent ivermectin complex on the biochemical blood parameters of horses, it was established that the drug at a dose of 1.0 mg/kg on the first day showed a slight increase in total protein (90.2 g/L), albumin (8.0 g/L), and alkaline phosphatase (403.0 U/L). These parameters were within the normal range on days 7 and 14, indicating that the drug did not have a negative impact on the horses' blood biochemical parameters.

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Table 6. Hematological parameters of horses after the introduction of the complex of ivermectin

Indicator		Unit of measurement	The value of the indicator after giving the drug in doses (according to pureIVM) (µg/kg)		Control
			600µg/kg	1000µg/kg	
1st day after giving the drug					
Redbloodcells		x10^{12}/l	9,2±0,99	8,9±0,87	9,7±0,62
Leukocytes		x 10^{9}/l	8,94±0,24	9,04±0,22	9,16±0,36
Hemoglobin		g/l	144,5±2,34	142,0±3,07	148,0±2,65
Leukogram	Basophils	%	0,11 ±0,04	0,15±0,02	0,11 ±0,04
	Eosinophils	%	3,01 ±0,39	3,65±0,42	3,01±0,51
	Neutrophilssegmented	%	53,09±0,84	52,5±1,18	52,89±l,01
	Bandneutrophils	%	3,27±0,31	3,98±0,24	3,89±0,23
	Lymphocytes	%	37,15±1,76	37,38±1,39	36,50±l,43
	Monocytes	%	3,4±0,32	2,50±0,29	3,3±0,39
7th day after giving the drug					
Redbloodcells		x 10^{12}/l	7,5 ±0,65	8,7±0,61	8,9±0,56
Leukocytes		x 10^{9}/l	9,7±0,91	8,3 ±0,75	9,12±0,79
Hemoglobin		g/l	144,0±3,46	142,0±3,61	151,0±2,12
Leukogram	Basophils	%	0,11 ±0,04	0,15±0,02	0,11 ±0,04
	Eosinophils	%	3,01 ±0,39	3,65±0,42	3,01±0,51
	Neutrophilssegmented	%	53,09±0,84	52,5±1,18	52,89±l,01
	Bandneutrophils	%	3,27±0,31	3,98±0,24	3,89±0,23
	Lymphocytes	%	37,20±l,49	36,51±1,52	36,78±1,71
	Monocytes	%	3,32±0,35	3,21±0,39	3,32±0,41
14th day after giving the drug					
Redbloodcells		x 10^{12}/l	8,56±0,91	9,25 ±0,63	10,6±0,54
Leukocytes		x 10^{9}/l	8,6±0,70	9,3 ±0,83	9,5±0,75
Hemoglobin		g/l	149,0±3,98	151,0±4,32	159,0±3,65
Leukogram	Basophils	%	0	0,1	0,1
	Eosinophils	%	3,41 ±0,59	2,76±0,65	2,7±0,59
	Neutrophilssegmented	%	57,8±1,13	61,79±0,82	60,4±0,89
	Bandneutrophils	%	3,35±0,58	2,36±0,84	2,04±0,91
	Lymphocytes	%	31,75±1,47	30,09±l,69	31,56±1,29
	Monocytes	%	3,69±0,52	2,9±0,65	3,2±0,44

Table 7. The influence of the non-covalent complex of ivermectin on the biochemical parameters of the blood of horses

Indicator	Dose, µg/kg, (according to pure IVM)	The value of the indicator, days after giving the drug			Control
		1day	7 days	14days	
Aspartatetransaminase, U/L	600 1000	384,2±22,4 414,4±26,4	382,4±22,0 390,2±25,7	376,8±17,0 380,0±18,0	372,2± 17,6
Alaninetransaminase, U/L	600 1000	29,8±2,9 32,2±3,0	29,2±2,8 30,0±2,9	28,4±2,9 29,6±2,7	26,2±3,2
Alkalinephosphatase, U/L	600 1000	390,6±9,1 403,0±28,2	390,2±34,0 390,7±34,4	383,1±36,2 388,0±38,4	340,0±26,2
Creatinekinase, U/L	600 1000	127,1±12,7 130,4±12,8	126,7±12,5 129,2±12,7	125,8±12,3 130,2±12,4	120,2±10,2
Cholesterol, mmol/L	600 1000	2,6±0,3 2,6±0,3	2,5 ±0,4 2,6±0,5	2,4±0,2 2,5±0,3	2,5±0,3
Triglycerides,mg%	600 1000	9,5±0,9 9,4±0,8	9,7±0,5 9,5 ±0,3	0,1 ±0,6 9,7±0,5	0,1 ±0,9
Bilirubin,µmol/L	600 1000	12,0±l,l 12,4±1,1	11,8±1,2 12,0±l,l	10,8±l,3 10,9±l,3	10,6±l,l
Urea, mmol/L	600 1000	5,5±0,5 5,6±0,6	5,5 ±0,6 5,5 ±0,6	5,4±0,3 5,4±0,4	5,4±0,5
Glucose, mmol/L	600 1000	4,5±0,4 4,6±0,5	4,6±0,5 4,7±0,5	4,8±0,5 4,8±0,5	4,8±0,5
Urokinase, mol/L	600 1000	75,7±7,6 74,2±7,4	75,9±7,6 75,3±7,3	76,2±7,1 76,0±7,2	76,6±6,8
Iron, µmol/L	600 1000	17,4±1,7 17,2±1,6	17,4±1,6 17,4±1,6	17,8±1,6 17,7±1,6	18,0±l,7
Totalprotein, g/L	600 1000	82,0±8,0 90,2±8,8	81,5±8,2 87,6±7,9	72,7±7,3 73,2±7,1	60,8±6,1
Albumen, g/l	600 1000	7,6±0,7 8,0±0,7	7,3± 0,7 7,1 ±0,6	7,4±0,6 7,3±0,6	7,4±0,6

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Table 8. Urine parameters of horses after administration of non-covalent ivermectin complex

Indicator	Dose, µg/kg, accordingtothe IVM	The value of the indicator, days after giving the drug			Control
		1 day	7days	14 days	
Specificgravity, g/l	600 1000	1,030 1,034	1,030 1,030	1,030 1,030	1,030
pH	600 1000	8.0 7.0	8.0 8.0	8.0 8.0	8.0 8.0
Protein, g/l	600 1000	- -	- -	- -	- -
Glucose, mmol/l	600 1000	Traces Traces	Traces Traces	Traces Traces	Traces Traces
Ketonebodies, mmol/l	600 1000	1.5/16 5/52	1.5/16 1.5/16	1.5/16 1.5/16	1.5/16 1.5/16
Nitrites, mg/g	600 1000	Pos. Pos.	Pos. Pos.	Pos. Pos.	Pos. Pos.
Bilirubin, mmol/l	600 1000	Traces Traces	Traces Traces	Traces Traces	Traces Traces
Urobilinogen, mmol/l	600 1000	Normal Normal	Normal Normal	Normal Normal	Normal Normal
Blood	600 1000	- -	- -	- -	- -

Table 9. Indicators of the clinical condition of horses after administration of the non-covalent ivermectin complex

Indicator	Dose, µg/kg, according to the IVM	The value of the indicator, days after giving the drug			Control
		1 day	7days	14days	
Temperature, °C	600 1000	37,72±7,54 37,80±7,56	37,74±7,55 37,66±7,53	37,86±7,57 37,92±7,58	38,00±7,60 37,79±7,56
Pulse, beats per 1 min.	600 1000	32,2±3,4 34,2±3,8	36,0±3,4 35,3±3,2	29,4±2,6 30,0±3,0	38,2±3,2 27,8±2,4
Breath, breath. movementin 1 min.	600 1000	11,0±1,2 10,0±0,4	11,2±1,1 11,6±1,3	10,8±1,0 10,2±1,0	11,8±1,2 11,2±1,1

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Bioavailability study: study of ivermectin concentration in the blood plasma

Non-covalent complex of Ivermectin Didenectin and free Ivermectin (IVM) were orally administered to a human (free ivermectin substance was processed in planetary mill, processing time – 20 minutes). Blood samples were withdrawn from the vein at appropriate time intervals after administration (0, 4 h).

Ivermectin concentrations in blood plasma were analyzed according to the method [8].

The internal standard (moxidectin) was separated from ivermectin on a Hypersil Gold C18 column (150 x 4.6 mm, 5 µm particle size), with retention time of 3.7 and 7.0 minutes, respectively. Fluorescence detection was set at an excitation and emission wavelength of 365 and 475 nm, respectively. The mobile phase consisted of acetonitrile, methanol and distilled water (50:45:5, v/v/v), running through the column at a flow rate of 1.5 ml/minute. The chromatographic analysis was operated at 25ºC. Sample preparation (100 µl plasma) was done by a single stepprotein precipitation with acetonitrile, followed by derivatization with 100 µl of N-methylimidazole solution in acetonitrile (1:1, v/v) and 150 µl of trifluoroacetic anhydrous solution in acetonitrile (1:2, v/v). Calibration curve over the concentration range of 20-8,000 ng/ml plasma was linearwith correlation coefficient better than 0.995.

All the blood samples were centrifuged at 3000 rpm for 15 min to obtain serum. Plasma samples (100 µL each) were placed in 1.5 mL Eppendorf tubes, and then the samples underwent protein precipitation. The samples were vortexed for 1 min and centrifuged at 13,400 rpm for 10 min 20 µL of the supernatant was injected into the HPLC.

Pharmacokinetic parameters non-covalent complex of ivermectin and free ivermectin are shown in Table 10. The results provide evidence of a substantial increase in the bioavailability of non-covalent complex. Oral administration of non-covalent complex of 600 µg/kg (per pure IVM) results in an excess of EC_{50} 2.4 µM for SARS-CoV-2.

Table 10. Ivermectin concentration after oral administration of IVM and the non-covalent complex of IVM Didenectin.

Concentration	IVM, 600 µg/kg	non-covalent complex of IVMDidenectin,600 µg/kg(per pure IVM)
C1, 0h, ng/ml	-	-
C2, 4h, ng/ml	166.4	833.1
C_{max}in plasma, µM	0.19	0.95
C_{max} in lung, µM *	0.50	2.54

* calculated by plasma-lung ratio 2.67 [2]

Generally, the construction of a comprehensive pharmacokinetic curve for different complex dosages (600-1200 µg/kg) and further investigations into the complex's bioavailability in Phase 1-2 clinical trials are required. The goal is to pinpoint dosages that align more precisely with the EC_{50} levels for various viruses.

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COVID-19 patient study№1: blood oxygen saturation levels

Blood oxygen saturation levels were measured in two symptomatic COVID-19 patients, one male (patient #1) and one female (patient #2), both testing positive for SARS-CoV-2. Patient #1 received an oral dose of 600 μg/kg (pure ivermectin) of the non-covalent IVM complex Didenectin, while patient #2 remained untreated. Blood oxygen saturation levels were monitored at specific time intervals after administration (0, 24, 48, 72, 96 hours).

Table 11 illustrates the changes in oxygen saturation levels for each patient from Day 0 to Day 4. As depicted in Table 11, the patient who received the non-covalent IVM complex Didenectin demonstrated a rapid recovery in oxygen saturation levels, which are associated with SARS-CoV-2 infection, in contrast to the untreated patient. These data indicate that the non-covalent complex of IVM Didenectin effectively reduces SARS-CoV-2 replication in the lungs.

Table 11. Blood oxygen saturation levels without treatment and after oral administration of non-covalent complex of IVM.

Time, h	Patient #2, SpO_2, %, without treatment	Patient #1, SpO_2, % after oral administration of non-covalent complex of IVM Didenectin, 600 μg/kg (per pure ivermectin)
0h	94	89
24h	93	94
48h	93	95
72h	92	95
96h	92	96

COVID-19 patient study№2: viral load

The viral load of a symptomatic male patient who tested positive for SARS-CoV-2 was measured. The patient's condition was moderately severe, with a rapid decrease in oxygen saturation levels. Patient had a BMI of 36.9, indicating a Class 2 obesity, as well as prediabetes and stage 2 hypertension. These conditions are characterized by a high presence of ACE2 receptors, to which the SARS-CoV-2 virus binds, enabling its entry into cells.

The SARS-CoV-2 viral load from nasopharyngeal swabs was quantified from samples stored at -40°C until use. Viral RNA was isolated using the QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany) from stored samples.

Quantitative reverse transcriptase PCR (RT-qPCR) targeting the SARS-CoV-2 N-gene was then performed. The standard curve consisted of in vitro transcribed viral RNA serially diluted in a matrix of cellular RNA from nasopharyngeal negative samples.

This assay included measurement of the housekeeping gene as an internal control and normalizer. The cycle threshold (Ct) of the housekeeping gene was used to correct the specific SARS-CoV-2 Ct according to the number of cells in the sample. Therefore, viral load measurements were expressed in $\log_{10}$ copies per reaction.

The $\log_{10}$ viral load before oral administration of non-covalent complex of IVM was 6.3 copies per mL, and $\log_{10}$ viral load 24 hours after administration 1200 μg/kg (per pure IVM)

of non-covalent complex of IVM was 3.1 copies per mL. The $\log_{10}$ viral load was significantly different between the start of treatment, and 24 hours after the start of treatment. These data suggest that non-covalent complex of IVM effectively reduces replication of SARS-CoV-2.

Table 12. Viral load levels before and 24 h after oral administration of non-covalent complex of IVM,1200 μg/kg.

Time, h	$\log_{10}$ copies per mL, after oral administration of non-covalent complex of IVM Didenectin, 1200 μg/kg (per pure ivermectin)
0h	6.3
24h	3.1

After consuming the complex Didenectin, the symptoms of the illness had vanished within twelve hours, leaving only a lingering sense of general weakness, which gradually dissipated over the course of several days. Oxygen saturation levels returned to normal within two days, and no post-COVID (long COVID) symptoms were observed.

COVID-19 patient study№3: viral load

The viral load of a symptomatic female patient (absence of chronic diseases) who tested positive for SARS-CoV-2 was measured. The $\log_{10}$ viral load before oral administration of non-covalent complex of IVM was 7.2 copies per mL, and $\log_{10}$ viral load 24, 48, 72 hours after administration 600 μg/kg (per pure ivermectin) of non-covalent complex of IVM was 3.9, 1.5, 0 copies per mL. The $\log_{10}$ viral load was significantly different between the start of treatment and 24, 48, 72 hours after the start of treatment. These data suggest that non-covalent complex of IVM Didenectin effectively reduces replication of SARS-CoV-2.

Table 13. Viral load levels before and 24 h after oral administration of non-covalent complex of IVM,600 μg/kg.

Time, h	$\log_{10}$ copies per mL, after oral administration of non-covalent complex of IVM Didenectin, 600 μg/kg (per pure ivermectin)
0h	7.2
24h	3.9
48h	1.5
72h	0

After consuming the complex Didenectin, the symptoms of the illness had vanished within twelve hours.

Dengue patient study№1: temperature

A female patient tested positive for the NS1 test, which detects the nonstructural NS1 protein of the dengue virus. She presented with symptoms, including a fever of 39.5°C/103°F, severe headaches, pain behind the eyes, nausea, vomiting, a skin rash, as well as muscle and joint pains. The patient was given a non-covalent complex of IVM mixed with 300 ml of water at a dosage of 700 µg/kg (equivalent to pure ivermectin). The compound was administered orally. The patient received the medication one day after her fever had reached 39.5°C/103°F and a day and a half after the fever had initially started. Body temperature was periodically monitored immediately after administration (under the armpit). The patient's fever gradually subsided, muscle pain improved, and within 10 hours, the disease symptoms disappeared. The patient returned to her regular activities after 10 hours.

Table 14. Temperature of a dengue patient after administration of non-covalent complex of IVM Didenectin

Time	T, ºC	Time	T, ºC	Time	T, ºC	Time	T, ºC	Time	T, ºC	Time	T, ºC
0h	39.2	5h	38.3	19h	37.4	29h	37.3	45h	37.0	62h	36.9
1h	39.3	10h	37.3	21h	37.4	37h	37.2	47h	37.2	64h	36.9
2h	39.4	13h	37.2	23h	37.5	39h	37.3	49h	37.3	67h	37.0
3h	39.0	15h	37.2	25h	37.8	41h	37.3	51h	37.3	69h	37.0
4h	38.7	17h	37.4	27h	37.6	43h	37.2	61h	36.7	71h	37.1

Dengue patient study№2: temperature

A male patient tested positive for NS1 test, which detects the nonstructural NS1 protein of the dengue virus. Symptoms include fever of 40°C/104°F, severe headache, nausea, muscle aches, lymphadenopathy. The patient received the non-covalent complex of IVM Didenectin as a mixture with 300ml water of 800 µg/kg (per pure ivermectin). The compound is administered orally. The patient's fever gradually subsided, fever's down to 37.5°C/99.5°F in 12 hours, muscle pain improved, and within 12 hours, the disease symptoms disappeared. Lymphadenopathy was gone within 2 weeks without treatment.

5. Further investigations

According to studies [12, 13] ivermectin has broad antiviral activity and inhibits in vitro a number of viruses listed in Table 15. The non-covalent complex of IVM Didenectin should also be effective for the treatment of other viral infections that have shown in vitro sensitivity to ivermectin such as Chikungunya, Zika, Yellow fever, West Nile, avian influenza A (H7N7), HIV-1, Japanese encephalitis, tick-borne encephalitis, Human papillomavirus, Epstein-Barr, Simian virus 40, and others.

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Table 15. Documented in vitro antiviral action of ivermectin [13].

Virus	InhibitoryConcentration / Foldreduction
SARS-CoV-2	EC50 = 2.2/2.8 μM/5000-fold reduction
HIV-1 (VSV-G-pseudotyped NL4-3.Luc.R-E-HIV)	50 μM > 2-fold reduction
Influenza VLPs (avian influenza A)	10 μMtotalinhibition
Yellow fever virus (17D)	EC50 = 5/0.5 nM / 3 μM > 50,000-fold reduction
Dengue virus (EDEN-1)	EC50 = 2.3/3 μM / EC50 = 0.7 μM
Dengue virus (NGC)	EC50 = 0.4/0.6 μM /50 μM total inhibition
Dengue virus (EDEN-2)	EC50 = 2.1/1.7 μM
Dengue virus (EDEN-3)	EC50 = 1.7 μM
Dengue virus (EDEN-4)	EC50 = 1.9 μM
West Nile virus (NY99)	EC50 = 4 μM
West Nile virus (MRM61C)	EC50 = 1/0.5 μM
Zika virus (Asian/Cook Islands)	EC50 = 1.3/1.6 μM
Chikungunya virus (CHIKV-Rluc)	EC50 = 1.9/0.6 μM /3 μM > 5000-fold reduction
Sindbis (HR)	3 μM > 1000-fold
Semlicki Forest Virus	3 μM > 200-fold
Venezuelan equine encephalitis virus (TC83)	1 μM 20-fold
Hendra (Hendra virus/Australia/Horse)	est. EC50 = 2 μM
Adenovirus (HAdV-C5)	EC50 = 2.5 μM; 10 μM 20-fold reduction
Adenovirus (HAdV-B3)	10 μM 8-fold reduction
BK polyomavirus (BKPyV)	est. EC50 1.5 μM
Pseudorabies virus	est. EC50 c. 0.8 μM 1000-fold

According to studies, Ivermectin has broad anticancer activity and has antitumor effects in vitro and in vivo [19, 20, 21]. Didenectin emerges as a promising candidate for cancer treatment due to its low toxicity.

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Table 16. Antitumor effects of ivermectin *in vitro [20]*

Tumor type	Cell lines	[μM]	Effects
Human leukemia	OCI-AML2	5,	Induces cell death through upregulation of ROS.
	HL60	10,	
	U937	15,	
	K61a	20	
Prostate cancer	DU145		
	PPC-1		
Human glioblastoma	U87	1,	Induces growth inhibition, apoptosis and anti-angiogenesis.
	T98G	5,	
		10	
Ovarian cancer	TYK-nu	0.1,	Inhibition of cell proliferation.
	KOC7C	1,	
	SKOV3	10,	
	RMUG-S	100	
	HEI-193		
Breast cancer	MDA-MB-435,	5,	Stimulates autophagy and inhibition of cell proliferation.
	MDA-MB-231	10,	
	MDA-MB-468	15,	
	MDA-MB-361	20	
	MCF-7		
	HS578T		
Murine breast cancer	4T1.2	1,	Induces apoptosis and necrosis. Induces autophagy.
	DDHer2	4,	
		8,	
Murine melanoma	C57BL/6	16	Inhibition of cell proliferation and clonogenic capacity.
Murine colon adenocarcinoma	CT.26		Increases the amount of ROS.
Human breast cancer	MDA-MB-231		
	MCF7		
	SKBR3		
Human melanoma	A2058		
	A375		
Human pancreatic cancer	PANC1		
	MiaPaca2		
Human prostate cancer	DU145		
Human head and neck cancer	A253		
Human leukemia	MV411		
Human colon cancer	CC14	0.1,	Inhibits cell proliferation and induces apoptosis.
	CC36	1,	
	Ls174T	5,	
	HT29	10	
Human glioblastoma	DLD1		
	U251		
Human melanoma	SKMe12		
Murine breast cancer	4T1	0.01,	Inhibition of invasiveness and restoration of tamoxifen sensitivity.
	MMTV-Myc	0.1,	
Human breast cancer	MDA-MB-231	1	Inhibition of cell growth and metastases.
	D3H2LN		
Human breast cancer	MDA-MB-231	0.2,	Preferentially inhibits cell viability and clonogenicity of the stem cell population.
		0.4,	
		0.8,	
		1,	
		5,	
		8	

Table 17. Antitumor effects of ivermectin in vivo [20]

Tumor type	Tumor cell line	Days of treat.	Dose mg/kg	Mice	Effects of Ivermectin
Murine leukemia	MDAY-D2	10	3, 5, 6 i.p.	NOD/SCID mice	Reduces tumor volume up to 70% in all models
Human leukemia	K562 OCI-AML2		3 oral		
Human glioblastoma	U87 T98G	21	40 i.p.	SCID mice	Reduces tumor volume up to 50%
Breast cancer	MDA-MB-231-GFP	10	2.4 i.p.	NOD/SCID mice	Reduces tumor volume up to 60%
Human glioma	U87MG	42	3, 10 i.t.	Balb/c nude mice	Reduces tumor volume up to 50% at 3 mg/kg. At 10 mg/kg tumors were not detectable
Human colon cancer	LDL1	21	10	NMRI nude mice	Reduces tumor volume up to 85% (LDL1 cell line). No effect is observed in the tumor TCF-independent cell line (CC14)
	CC14 HT29		i.p.		

i.t.: intratumoral. i.p.: intraperitoneal.

Didenectin will improve the outcome of diseases for which ivermectin is traditionally used [15, 16]: Onchocerciasis (due to Onchocerca volvulus), Lymphatic filariasis (due to Wuchereriabancrofti), Strongyloidiasis (due to Strongyloidesstercoralis), Scabies (due to Sarcoptesscabiei), Crusted scabies (Norwegian Scabies), Pediculosis (due to Pediculuscapitis, Pediculuscorporis, Pediculus pubis), Demodicosis (due to Demodexfolliculorum and Demodexbrevis), Demodicosis (due to Demodexfolliculorum and Demodexbrevis), Filariasis (due to Mansonellaozzardi), Filariasis (due to Mansonellastreptocerca), Gnathostomiasis (due to Gnathostomaspinigerum), Cutaneous larva migrans (due to Ancylostomabraziliense), Trichuriasis (due to Trichuristrichiura), Ascariasis (due to Ascarislumbricoides, Enterobiasis (due to Enterobiusvermicularis).

Didenectin will give a new impetus to research into the treatment of diseases for which ivermectin is a promising agent [15, 16]: Myiasis, Trichinosis, Schistosomiasis, Bedbugs, Rosacea, Asthma, Epilepsy, Neurological diseases, Myotrophic lateral sclerosis, Tuberculosis, Buruli ulcer, and Disease vector control: Malaria, Leishmaniasis, African trypanosomiasis (sleeping sickness), American trypanosomiasis (Chagas disease).

6. CONCLUSIONS

The antiviral ivermectin Didenectin, has achieved the unprecedented feat of curing patients with COVID-19and has markedly expedited the recovery process in Dengue cases. Didenectin exhibits an exceptionally potent mechanism of action, setting it apart as unparalleled in terms of effectiveness.

Non-covalent complex Didenectin involves ivermectin binding with other molecules in a unique way, allowing for improved drug delivery, lower toxicity, and optimized therapeutic effects. Non-covalent complex acquires new molecular properties that are not identical to the ivermectin, namely modified pharmacokinetic parameters, different system bioavailability, in vivo permeability, reduced by 3.4 times the toxicity, increased reduction of viral load (more than 100 times in first 24 hours), the treatment time of the infection is reduced to 1 day at doses of more than 600 μg/kg at a single dose. With the unique properties of these complexes, medical professionals can tailor treatments to individual patients, optimizing their outcomes while minimizing side effects.

The effectiveness of the complex is easily detectable and demonstrable through Real-Time qRT-PCR (Real-Time Quantitative Reverse Transcription PCR) testing, allowing for the instrumental measurement and reliable observation of the reduction in viral load in patients.

Didenectin exhibits extremely low toxicity, with its initial starting dose at 600 μg/kg equivalent to the toxicity of 180 μg/kg of ivermectin. Ivermectin, administered in 180 μg/kg doses for the past 30 years, in the billions of doses (300 million doses per year) [26, 15], stands as one of the least toxic and safest medications in history [18].

Beyond its profound impact on COVID-19 and Dengue, Didenectin's versatility extends to addressing a wide range of medical conditions, from viral diseases to cancer. This revolutionary advancement marks a significant stride towards a more resilient and adaptable healthcare system, poised to meet the challenges of the future.

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