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# Results of the Application of Pharmacological in Silico Base Structures in Studies of Endothelioprotective Properties of Drugs for The Treatment of Coronavirus Infection (Covid-19)

Kanistov Vasil Lyubenov*

*Department of Pharmacology and Clinical Pharmacology, Medical Institute, Belgorod State National Research University. Russia.*

***Corresponding Author**: Kanistov Vasil Lyubenov, Department of Pharmacology and Clinical Pharmacology, Medical Institute, Belgorod State National Research University. Russia.

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## Abstract

Identifying the results of the application in silico of the basic structures, in the study of the endothelial proprotective properties of drugs for the treatment of coronavirus infection (COVID-19), affecting the pharmacological targets of the cardiovascular system (CVS). Researchers in the field of theoretical and experimental pharmacology and medicine. We accept the physico-mathematical model "damper-spring" as a theoretical and experimental justification for the development of methods for mathematical modeling in silico of basic structures, for studying the endothelioprotective properties of drugs. We introduce theoretical and experimental development in silico of basic structures in the study of endothelioprotective properties of drugs for the treatment of coronavirus infection (COVID-19). Established by the experimental pathway influence of endothelial function and values of cost in silico coefficients and $\mathbf{c_i d_i}$ antiviral drugs used to treat coronavirus infection COVID-19 based on ATC (Anatomical-Therapeutic-Chemical) classification of drugs. It has been shown that the effective strength$\mathbf{P_e = f2}$ depends on the potentially positive and / or negative effects of the function of endotheliocytes, smooth muscle cells (MMC) and the vessel wall on the state of homeostasis and the activity of pharmacological targets of the cardiovascular system (CCC). A, numerical values and (mechanical and chemical effects) are included in the models **cd in silico** of the basic structures for the study of endothelioprotective properties of medicinal products. A calculation of the numerical value of the indicators of the coefficients is$c_i d_i$ made both by formula and ATC. A connection has been established between the pharmacological coefficients and $\mathbf{W_{СМЩ}(p) = \frac{d}{2.c+d}}$ (16) $\mathbf{Kf2_i}$the values **in silico** coefficients and$\mathbf{c_i d_i}$ , to varying degrees of deterioration / improvement in the function of endotheliocytes, smooth muscle cells (MMC) and the vessel wall, as pharmacological targets of the cardiovascular system (CCC). The model of endothelial function/dysfunction on which experimental studies are still being conducted in pharmacology and medicine in the form of an unbalanced scale is inherently inaccurate. Research processes of fundamental pharmacology and medicine. Applications of pharmacological **in silico** base structures in the study of the endothelial proprotective properties of drugs for the treatment of coronavirus infection (COVID-19) in the research processes of fundamental pharmacology and medicine can be done (only) under the supervision of interdisciplinary specialists.

***Keywords:*** *in silico basic structures, endothelioprotective properties of drugs, tuning coefficients* $\boldsymbol{c_i}$ *and* $\boldsymbol{d_i}$*, mathematical modeling, endothelials, endotheliocytes, smooth muscle cells (MMC), vessel walls, cardiovascular system (CVS), coronavirus infection (COVID-19).*

## Introduction

In the past few years, it has been argued that clinical trials on the in-silico model are effective as pharmacological targets of the cardiovascular system (CCC). An in silico clinical trial is conducted as an individual computer simulation used in the development or normative evaluation of a drug, device or intervention.

This kind of model (as in silico) makes it possible to study the behavior of the system when internal characteristics and external conditions change, to create and implement scenarios, to solve the optimization problems of the aggregate system. However, in each computer implementation of the model, a specific biological identification corresponds to the constantly changing pharmacological targets of the cardiovascular system (CCC). so-called tuning coefficients. And this, very much complicates on its turn the mathematical model.

Up to the point of this scientific study, there are problems: - Completely simulated clinical trials in silico, the basic structures affecting pharmacological targets of the cardiovascular system (CCC) are impossible with the application of modern technologies and today's understanding of the ongoing processes in biological structures. But, after applying this new methodology of mathematical modeling of the endothelium and as a result of this study, in silico model development is expected to have significant advantages over current **in vitro**, **ex vivo** and **in vivo** clinical trials – and research in this area is ongoing [1].

The endothelium, together with the vascular wall of the artery and vein, is an integral (holistic) organ, capable of responding to mechanical action ("for example, cyclic stretching or fluid shift tension): flowing blood, the amount of blood pressure in the lumen of the vessel and the degree of tension of the muscular layer of the vessel" [2].

In the pharmacological study of biological objects, many models have been created for all these processes. It seems that for each study a special model is created to confirm a certain theoretical prediction. Today, at least there is no single universal model on which to conduct all pharmacological experiments!

## Materials And Methods

### A. Physical and mathematical model "damper-spring" [3] as a theoretical and experimental justification for the development of methods for mathematical modeling in silico of basic structures, for the study of endothelioprotective properties of drugs.

The reaction of endotheliocytes and smooth muscle cells (MMC) vessel wall to the cardiovascular system **(**CCC) to mechanical and chemical influences leads us to apply the mechanical model "damper-spring" (Figure 1).

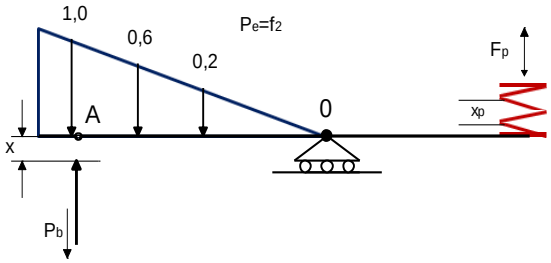


***Fig 1:*** Mechanical model in the form of a "damper-spring" on the physico-biological control object (FBOU) - the forces of blood pressure and blood elements on endotheliocytes, smooth muscle cells (MMC) and the walls of the vessel of the cardiovascular system (CCC).

At the right end of the flap by the model we have a spring, which is calculated by the equation according to Hooke's law:

$$\mathbf{F_p} = -\mathbf{k_p}.\mathbf{x_p} \qquad (1)$$

Where: - moving the end $\mathbf{x_p}$**of the B** turns to the spring and - the stiffness of the spring $\mathbf{k_p}$

Since in our case the spring is compressed, the equation takes the form:

$$\mathbf{F_p} = \mathbf{k_p}.\mathbf{x} \qquad (2)$$

This force is called the "$\mathbf{F_p}$blood vessel constriction force", which is right proportional to the value of the resistance of the elastic fibers (the inner elastic membrane and the outer elastic membrane of the vascular wall of the artery and vein) and is directed in the opposite direction to the pressure () of the blood vessels.$\mathbf{\Delta P}\mathbf{\Delta P} = \mathbf{P}$ артериальное $- \mathbf{P}$ венозное $= \mathbf{Q}.\mathbf{R}$

At the left end of the flap the model, of t. **0** to t. **A** have distributed blood pressure forces ($\mathbf{\Delta P}$mechanical and chemical effects on the walls of blood vessels) and as a result, the value of tuning coefficients according to **the in-silico** model$\mathbf{c_3} = \mathbf{0,2}$**:** (stronger than active), $\mathbf{c_2} = \mathbf{0,6}$ (average active) and (weakly active). And corresponding values (weakly active$\mathbf{c_1} = \mathbf{1,0}\mathbf{d_1} = \mathbf{1,0}$**),** $\mathbf{d_2} = \mathbf{0,6}$ (average active) and (stronger active). $\mathbf{d_3} = \mathbf{0,2}$

The effective force of value $\mathbf{c_1}$**,** $\mathbf{c_2}$ and$\mathbf{c_3}$ **(**$\mathbf{d_1}$**,** $\mathbf{d_2}$ and$\mathbf{d_3}$ **)** is$\mathbf{P_e} = \mathbf{f2}$ the force that acts in t. **A** flap and is directed in the opposite direction - "the force of narrowing the blood vessel".$\mathbf{F_p}$

In the specific case, the numerical values and (mechanical and chemical effects) is the collection of suma from all coefficients indicating the degree and direction of activity $\mathbf{cd}$of the pharmacological targets of the

cardiovascular system (CCC) on the functions of endotheliocytes, smooth muscle cells (MMC) and the vessel wall to deterioration or to improvement. We can write:

$$\sum_{i=1}^{n} c_i = c_1 + c_2 + c_3 + \cdots c_n \quad (3)$$

$$\sum_{i=1}^{n} d_i = d_1 + d_2 + d_3 + \cdots d_n \quad (4)$$

For a mechanical model in the form of a "damper-spring" on a physico-biological control object (FBOU) (Figure 1), we will make a mathematical model in dynamics, with a differential equation, in the form of [3]:

$$x(t) = \frac{d}{c+d}.e(t) - \frac{c}{c+d}.y(t) \quad (5)$$

Looking at equation (3) and equation (4), equation (5) takes the form:

$$x(t) = \frac{\sum_{i=1}^{n} d_i}{\sum_{i=1}^{n} c_i + \sum_{i=1}^{n} d_i}\, e(t) - \frac{\sum_{i=1}^{n} c_i}{\sum_{i=1}^{n} c_i + \sum_{i=1}^{n} d_i}\, y(t) \quad (6)$$

Note: The values - with a conditionally negative effect on the $c_i$functions of endotheliocytes, smooth muscle cells (MMC) and the vessel wall include both cyclic stretching and fluid (blood) shear tension. The values include all elements with a conditionally positive effect on $d_i$the functions of endotheliocytes, smooth muscle cells (MMC) and vessel walls, including both cyclic stretching and fluid (blood) shear tension.

Thus, the cost (Figure 1) of the effective strength $P_e = f2$ depends on the potentially positive and/or negative effects of the function of endothelial cells, smooth muscle cells (MMC) and the vessel wall on the state of homeostasis and activity pharmacological targets of the cardiovascular system (CCC). A, numerical values and (mechanical and chemical effects) are included in **cd in silico** models of basic structures for the study of endothelioprotective properties of medicines.

**B. Theoretical and experimental development in silico of basic structures in the study of endothelioprotective properties of drugs for the treatment of coronavirus infection (COVID-19).**

Using the ATC (Anatomical-Therapeutic-Chemical) classification of drugs [4], we will build **in silico** models to study the endothelioprotective properties of drugs for the treatment of coronavirus infection (COVID-19).

Note: ATC (Anatomical-Therapeutic-Chemical) classification. Full English name - Anatomical Therapeutic Chemical Classification System (ATCCS) [4]. Taking into account the side effects, drug interactions and contraindications for experimental and literature data on conditionally antiviral drugs used to treat coronavirus infection COVID-19, we introduce coefficients **c** and **d**.

Where the coefficient **c** indicates: Potential negative effect of the drug substance on endothelial function, and coefficient **d** indicates: Potential positive effect of the drug substance on endothelial function. (Table 1)

***Table 1:*** Potential positive and negative effects on endothelial function (EF) of medicinal substance drugs used to treat COVID-19 coronavirus infection

| Coefficient/Value | Activity | Endothelial function |
|---|---|---|
| $c_1 = 1,0$ | inactive | leads to a low degree of deterioration in endothelial function. |
| $c_2 = 0,6$ | average active | leads to a moderate deterioration in endothelial function. |
| $c_3 = 0,2$ | stronger active | leads to a high degree of deterioration in endothelial function. |
| $d_1 = 0,2$ | inactive | leads to a low degree of improvement in endothelial function. |
| $d_2 = 0,6$ | average active | leads to an average improvement in endothelial function |
| $d_3 = 1,0$ | stronger active | leads to a high degree of improvement in endothelial function |

Note: Values are immeasurable coefficients 0.2; 0,6; 1.0 represent in its essence pharmacological activity a drug substance to the functional state of the endothelium. It should be noted that in the pharmacodynamic and pharmacokinetic processes occurring in the body after taking the drug, there is practically no "0" state in tissues and cells. For this reason, our minimum state is not zero "0", but "0.2".

Consistently and step by step we introduce $c_i$ and$d_i$ **- degrees** and direction of activity pharmacological targets of the cardiovascular system (CCC) (Figure 1) the embarrassing effect of SMS. 2 (), in the form of pharmacological coefficients (Table 1 and Table 2) are represented by the equation: $f2\ Kf2_i$(7) и (9)

$$\mathbf{Kf2_i} = \frac{\mathbf{d_i}}{\mathbf{2.c_i + d_i}} \qquad (7)$$

Where: $\mathbf{c_i}$ and$\mathbf{d_i}$ **- degrees** and direction of activity pharmacological targets of the cardiovascular system (CCC), numerical coefficients (0.2, 0.6, 1.0)

$\mathbf{Kf2_i}$ **-** Pharmacological coefficients, calculated by the formula equation () are presented as 7an embarrassing effect of CMS. 2 () in Figure 1.$\mathbf{f2}$

$\mathbf{i = 1, 2, 3}$ - low degree of deterioration of endothelial function.

$\mathbf{i = 4, 5, 6}$ - a high degree of deterioration in endothelial function.

$\mathbf{i = 7}$ - "at the boundary of stability" = moderate deterioration of endothelial function

$$\mathbf{Kf2_1 = 0.09900990099} \ldots.$$

$$\mathbf{Kf2_2} = 0{,}142857142857$$

$$\mathbf{Kf2_3} = 0{,}230769230769 \ldots$$

$$\mathbf{Kf2_4 = 0,71428571428} \ldots.$$

$$\mathbf{Kf2_5} = 0.6$$

$$\mathbf{Kf2_6} = 0.45454545 \ldots$$

$$\mathbf{Kf2_7 = 0.333333} \ldots.$$

## Results And Discussion

Looking for a transfer function of embarrassing effects ($\mathbf{f2}$the effective force $\mathbf{P_e = f2}$ of potentially positive and/or negative effects of endotheliocyte function, smooth muscle cells (MMC) and vessel walls on the state of homeostasis and the activity of pharmacological targets of the cardiovascular system (CVS)):

$$\mathbf{W(p)} = \frac{\mathbf{Y(p)}}{\mathbf{X(p)}} = \frac{\mathbf{W_1(p)}}{\mathbf{1 + W_2(p)}} \qquad (8)$$

Replace$\mathbf{W_1(p) = A} = \frac{\mathbf{d}}{\mathbf{c+d}}$ and$\mathbf{W_2(p) = B} = \frac{\mathbf{c}}{\mathbf{c+d}}$

Get:$\mathbf{W(p) = k_{f2}} = \frac{\mathbf{d}}{\mathbf{2.c+d}} = \mathbf{W_{СМЩ}(p)}$

$\mathbf{k_{f2}}$ **- is a pharmacological coefficient -** with a potentially negative or positive effect of pharmacological targets of the cardiovascular system (CCC).

$$\mathbf{W_{СМЩ}(p)} = \frac{\mathbf{d}}{\mathbf{2.c + d}} \qquad (9)$$

See equation (5): $\mathrm{x(t)} = \frac{\mathrm{d}}{\mathrm{c+d}}\ \mathrm{e(t)} - \frac{\mathrm{c}}{\mathrm{c+d}}\ \mathrm{y(t)}$

We get**:**

$$\mathbf{k_{f2}}\ (\mathbf{0,3333333333333333} \ldots\ \div\ \mathbf{0,7142857142857143} \ldots . . \div\ \mathbf{0,0909090} \ldots)$$

Where:$\mathbf{c = 0,2; 0,6; 0,8; 1,0}$ **-** Potential negative effect of pharmacological targets of the cardiovascular system (CVS) on the function of endotheliocytes, smooth muscle cells (MMC) and the vessel wall.

$\mathbf{d = 0,2; 0,6; 0,8; 1,0}$– Potential positive effect of pharmacological targets of the cardiovascular system (CCC). on the function of endotheliocytes, smooth muscle cells (MMC) and vessel walls.

It's easy to notice what makes sense when i.e., $\mathbf{W(p)2.c + d} \neq \mathbf{0}[-\mathbf{c}] < \frac{\mathbf{d}}{\mathbf{2}}$

Thus, the potential negative effect of pharmacological targets of the cardiovascular system (CVS) on the functions of endotheliocytes, smooth muscle cells (MMC) and the vessel wall should not exceed half the absolute value of the potential positive effect of pharmacological targets of the cardiovascular system (CVS).

Applying the equations and values from the tables (Table 1) and (Table 2): Consider(7) и (9) obtaining the results from **the application in silico** of the model of basic structures for the study of endothelioprotective properties of drugs used to treat coronavirus infection COVID-19 based on **ATC (**Anatomical-therapeutic-chemical**)** classification of drugs (Table 3):

***Table 2:*** Numerical values of pharmacological coefficients depending on $\mathbf{k_{f2}}$**ithe value of in silico** coefficients and as $c_i d_i$pharmacological targets of the cardiovascular system (CCC).

| **in silico коэффициенты** $\mathbf{ис_i d_i}$ | $\mathbf{d_3 = 1,0}$ **stronger active** | $\mathbf{d_2 = 0,6}$ **average active** | $\mathbf{d_1 = 0,2}$ **inactive** |
|---|---|---|---|
| $c_3 = 0{,}2$ stronger active | $Kf2_7 = 0.333333$ .... | $Kf2_5 = 0.6$ | $Kf2_4 = 0{,}71428571428$ .... |
| $c_2 = 0{,}6$ average active | $Kf2_2 = 0{,}142857142857\ldots$ | $Kf2_7 = 0.333333$ .... | $Kf2_6 = 0.45454545$ ... |
| $c_1 = 1{,}0$ inactive | $Kf2_1 = 0.09900990099$ ... | $Kf2_3 = 0{,}230769230769$ ... | $Kf2_7 = 0.333333$ .... |

***Table 4:*** Effect of endothelial function values of **the in-silico** model of antiviral drugs used to treat coronavirus infection COVID-19 based on ATC **(**Anatomical-Therapeutic-Chemical**)** classification of drugs and their values.

| **№** | **Name Drug** | **Classification: by ATC** | **модели in silico** and their meanings | **Influence of endothelial function** |
|---|---|---|---|---|
| 1. | Hydroxychloroquine and Chloroquine | P01BA02 | $\mathbf{c_3 = 0,2}$ | High degree of deterioration |
| 2. | Lopinavir and Ritonavir | J05AR10 | $\mathbf{c_3 = 0,2}$ | High degree of deterioration |
| 3. | Adalimumab | L04AB04 L01XC07 | $\mathbf{c_2 = 0,6}$ | Medium degree of deterioration High degree of deterioration |
| | Bevacizumab | L04AC07 | $\mathbf{c_3 = 0,2}$ | Moderate deterioration |
| | Тоцилизумаб* (Атлизумаб) | | $\mathbf{c_2 = 0,6}$ | |
| 4. | Corticosteroids: Methylprednisolone, combinations | H02BX H02BX01 | $\mathbf{c_3 = 0,2}$ | High degree of deterioration |
| | Dexamethasone, combinations | QH02BX90 | $\mathbf{c_2 = 0,6}$ | Moderate deterioration |
| 5. | Tofacitinib | L04AA29 | $\mathbf{c_3 = 0,2}$ | High degree of deterioration |
| 6. | Baricitinib | L04AA37 | $\mathbf{c_3 = 0,2}$ | High degree of deterioration |
| 7. | Ruxolitinib | L01XE18 | $\mathbf{c_2 = 0,6}$ | Moderate deterioration |
| 8. | Interferons: Interferon alfa-2b | L03AB L03FROM01 | $\mathbf{c_3 = 0,2}$ | High degree of deterioration |
| | Interferon beta-1 alpha | L03AB02 | $\mathbf{c_3 = 0,2}$ | High degree of deterioration |
| 9. | Remdesivir | CAS:1809249-37-3 | $\mathbf{c_2 = 0,6}$ | Moderate deterioration |
| 10. | Favipiravir | J05AX27 | $\mathbf{c_1 = 1,0}$ | Low degree of deterioration |
| 11. | Ribavirin | J05AP01 | $\mathbf{c_2 = 0,6}$ | Moderate deterioration |
| 12. | Chlorprothixen | N05AF03 | $\mathbf{c_2 = 0,6}$ | Moderate deterioration |
| 13. | Camostat | B02AB04 | $\mathbf{c_1 = 1,0}$ | Low degree of deterioration |
| 14. | Mepolizumab | R03D | $\mathbf{c_1 = 1,0}$ | Low degree of deterioration |
| 15. | Convalescent plasma | - | $\mathbf{c_1 = 1,0}$ | Low degree of deterioration |
| 16. | Antibodies to Spike | - | $\mathbf{c_1 = 1,0}$ | Low degree of deterioration |
| 17. | Immunoglobulins, | - | $\mathbf{c_1 = 1,0}$ | Low degree of deterioration |

We will compile and present in tabular form the relationship between pharmacological coefficients and $\mathbf{k_{f2}}$**i**values **in silico** coefficients and, $\mathbf{c_i d_i}$ to varying degrees of deterioration in the function of

endotheliocytes, smooth muscle cells (MMC) and vessel walls, as pharmacological targets of the cardiovascular system (CCC). (Table 4)

***Table 4 (2):*** Numerical values pharmacological coefficients and associations $\mathbf{k_{f2}i}$of the degree of deterioration in the function of endotheliocytes, smooth muscle cells (MMC) and vessel walls, as pharmacological targets of the cardiovascular system (CCC).

| **Pharmacological coefficients $\mathbf{Kf2_i}$** | **Values in silico coefficients and$\mathbf{c_i}$ $\mathbf{d_i}$** | | | | | |
|---|---|---|---|---|---|---|
| | $\mathbf{c_1 = 1,0}$ | $\mathbf{c_2 = 0,6}$ | $\mathbf{c_3 = 0,2}$ | $\mathbf{d_1 = 0,2}$ | $\mathbf{d_2 = 0,6}$ | $\mathbf{d_3 = 1,0}$ |
| $\mathbf{Kf2_1}$ | + | | | | | + |
| $\mathbf{Kf2_2}$ | | + | | | | + |
| $\mathbf{Kf2_3}$ | + | | | | + | |
| $\mathbf{Kf2_4}$ | | | + | + | | |
| $\mathbf{Kf2_5}$ | | | + | | + | |
| $\mathbf{Kf2_6}$ | | + | | + | | |
| $\mathbf{Kf2_7}$ | | | + | | | + |
| $\mathbf{Kf2_7}$ | | + | | | + | |
| $\mathbf{Kf2_7}$ | + | | | + | | |

## Conclusion

Let's summarize the results of the study - evaluate and experimentally determine the conditions for the implementation and directions of the way of application pharmacological coefficients$c_i$ and$d_i$:

The first group of drugs with **an in-silico** coefficient () $\mathbf{c_3 = 0,2}$of pharmacological activity of the drug substance to the functional state of the endothelium include: Hydroxychloroquine and Chloroquine; Lopinavir and Ritonavir; Bevacizumab, Methylprednisolone, combinations, Tofacitinib, Baricitinib, Interferon beta-1alpha and Interferon alfa-2b.

Their use in clinical practice can lead to a **high degree of deterioration in endothelial function** - quickly lead to endothelial dysfunction (ED).

The second group of drugs with **an in-silico** coefficient () $\mathbf{c_2 = 0,6}$of pharmacological activity of the drug substance to the functional state of the endothelium include: Adalimumab, Tocilizumab (Atlizumab), Dexamethasone, combinations, Ruxolitinib, Remdesivir, Ribavirin and Chlorprothixen.

Their use in clinical practice can lead to **an average degree of deterioration in endothelial function**. – Slowly lead to endothelial dysfunction (ED).

The third group of drugs with **an in-silico** coefficient () $\mathbf{c_1 = 1,0}$of pharmacological activity of the drug substance to the functional state of the endothelium include: Favipiravir, Camostat, Mepolizumab, Convalescent plasma, Antibodies to Spike and Immunoglobulins.

Their use in clinical practice can lead to a low degree of deterioration in endothelial function - practically **not lead to endothelial dysfunction** (ED).

Thus, the coefficients (**$c_1$, $c_2$** and **$c_3$;** $d_1$, **$d_2$** and **$d_3$**) in the application of pharmacological **in silico** basic structures in the study of endothelioprotective properties of drugs for the treatment of coronavirus infection (COVID-19), are active pharmacological coefficients. Which can be taken as pharmacological coefficients in future research in fundamental pharmacology and medicine on the physico-biological objects of control of the FBOU (endotheliocytes + smooth muscle cells (MMC) and vessel walls), physico-biological systems of automatic regulation (FBSAR) and homeostasis of the cardiovascular system (CCC).

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