HOW DID INFOMATICS BEGIN?

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Abstract: Informatics is a science for researching methods and processes for event, storing, treatment, analysis and estimation of the information, giving of opportunities to use it for taking decisions. It includes disciplines, concerning processing of information in the computers and computer networks. It learns: the information from a point of view of its structure, numerical characteristics, shapes and ways of reviewing; the information processes, as a composition of the main information events, also the methods and the instruments for their automation.

Keywords: informatics, etymology, informatics structure, information resources, Sumerian abacus, calculating watches, Pascaline, jukebox, electro-mechanical digital computers, computer Z1, British Colossus, Computer Atanasoff-Berry, ENIAC, Generations of computers.

Introduction

Explorative topics concerning the informatics: What can and what cannot execute in programs and database, how finds solution about specific calculation and informational tasks with maximum effectiveness, in what format should be safe an restore the information from definite type (structure and database), as programs and the people who have to communicate each other (user interface with program languages, review of knowledge) etc.

The Informatics' origin is tightly connected with mathematics, linguistic, the electronic engineering, and other sciences. During the last third of XX century it is approve as a own discipline, processing own methods and terminology.

1. Etymology

The concept "information" is primary concept, and its name comes from the Latin word "information" [1]. For the ancient Romans this word mean "imagination", "notion". Distinguishing to our days, its meaning changes to "message", "sending the message", to become a "measure of identity". In most open sense, the word "information" means records for the

surrounding reality, for the processes and the events, which are around us. The term "information" is using in different areas of the human knowledge. The psychology is interested from the information and its meaning in the way of communication. The cyberneticists saw the information from the process point of view and the controlling and its meaning during making of different managing decisions. In the communication systems is significant the quantity and measuring of the information. The already assumed information allows opening the learning about the different objects and processes. In his theory Cloth Shannon looks the information as an instrument which decrease the inconclusiveness of the things.

The word "informatics" is made from "inform", "information", and "ethics" from "automatics". In English, French, Russian and German languages in 1960 year starts a tendency of replacing the term "documentation" with terms, which have in their base the word "Information" [2]. The term in German "Informatik" was integrated by the German specialist Karl Steinbuch in his article "Informatik": Automatische Informations verarbeitung (Informatics: Automatic informatics processing) 1957 year. [3]

In English the term for "documentation" as is defined from the executing burro of the association of the special libraries of the USA, is understanding that creating, sharing, and using of documents – storing information, on aperture cards, microfilms, magnetic tape [4]. It was replaced by the term "science information" (informatics sciences). It is believed, that the term "informatics" independently of the other researchers is integrated by Walter F. Bower, founder of "Informatics Inc".

It is important for us to know, that in this district is reign by factionalism. Until now, the meaning of the subject "computer sciences" (because is using the modern scientific and methodological literature) is still not confirmed and settled by the community. This is a historic record, dating since the time of appearance the computers.

For now is settled that in Europe "computer science" is called "informatics", but at this moment in USA with this word are connected, applied calculations or data and their redaction in the context of other areas [5] as bio informatics, and geo informatics.

The concept of the science is also so difficult for the common definition, as a difference for example we can give the conception of the mathematics. This is a science of applied researching, as in the area of interdisciplinary researching, and is also academic.

Despite the fact, that the informatics is comparatively new science, its origin is fastened with the work Leibnitz.

2. Informatics structure
The informatics is separated on several sections.
2.1. Theoretical informatics
It teaching of the theory about the formal languages and automats, the theory of calculable and complexity, theory of columns, cryptology, logics (including predicative logic), official semantic and also is also securing the developing of the programming languages, compilers.
2.2. Practical informatics
The practical informatics gives the basic conceptions for solving standard problems as storing and managing of information, using databases, constructing of algorithms, models of solutions of common and complex tasks. Examples for this are the algorithms for sorting and fast transforming of Fourier.

One of the centered topics of the science is the practical software engineering. This is a systematic process of developing of the idea of the ready software.
2.3. Technical informatics
The technical informatics occupies the hardware and the computer technologies, and serves as a platform of microprocessors, computer structures and distributing systems. On this way, it provides a connection with the electrical engineering. A computer informatics is a science, which

studies the concept of building computers. It defines and optimizes the interaction between microprocessor, memory and peripheral controllers. Other accent is the connection between the machines. This gives electronic data exchange between computers, and therefore is a technical fundament for the Internet for developing of routers, switches and firewalls. This discipline includes developing and standardizing of the Network protocols as TCP, HTTP or SOAP for data exchange between the different machines.

2.4. Applied informatics

The applied informatics integrates specific applications of the computer sciences in different areas of the fiction or productivity, for example: business informatics, geo informatics, computer linguistic, bio informatics etc.

2.5. Natural informatics

The natural informatics is a science tendency and the researches are pointed in processing of the information in the nature, the brain and human society. It lays on such classic researching areas as theory of evolution, morphogenesis and developing of the biology, systems of scientific researching, brain testing, DNA, theory for control and behavior in a social group, history etc.[6].

3. Calculating devices
3.1. Early calculating devices

First calculating instruments are probably sticks, which still are using in many schools at the beginner grade for count. During the time they become more complicated, for example, like Phoenician clay figures which are intended to visualize the amount, as a convenience are situated in special containers.
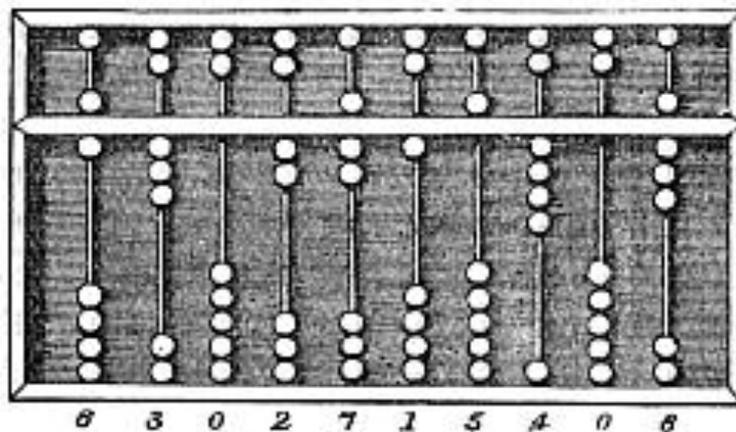
Pic. 1. Abacus

The Sumerian abacus appeared between 2700 and 2300 BC. It held a table of successive columns which delimited the successive orders of magnitude of their sexagesimal (base 60) number system [7].

These devices (*plural* abaci or abacuses) are using by the merchants and the counters before. Gradually, from the simplest devices for counting are born a lot and more complicated machines: the Abacus Logarithmic ruler, the mechanical computer.

The Antikythera mechanism (/ˌæntɪkɪˈθɪərə/ AN-tih-kih-THEER-ə) is an Ancient Greek hand-powered orrery, described as the oldest known example of an analogue computer [1-3] used to predict astronomical positions and eclipses decades in advance [4-6].

It could also be used to track the four-year cycle of athletic games which was similar to an Olympiad, the cycle of the ancient Olympic Games [7-9].

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Pic.2. Derek J. de Solla Price (1922–1983) with a model of the Antikythera mechanism.

Despite the simplicity of the earliest computer devices, an experienced counter can achieve a result of simple count even faster, than an owner of a modern calculator.

Of course, the productivity and the speed of the modern computer machines is a long out of the capacity of the famous human calculators.

In 1623 in Germany Wilhelm Schickard is created such called "calculating watches, which is marked as the first automatic calculators. In the letters sent to Johannes Kepler he explains, how is possible to use the device for counting of astronomical tables. The machine of Schikard, is able to add and deduct 6 letters code, alarming with sound after overfilling. In 1960 on the base of the survived sketches is made a copy of the calculator, which confirms its existence and functioning.

In 1642 a machine which helps with the calculating of numbers is invented by the great French scientist Blaise Pascal. "Pascaline", as the creator is called it, is a mechanical device, which represents a box, full with a number of elements and has worked with typing the numbers 0-9 and has calculated with the help of a rolling handle.

Pic. 3. Summing machine of Pascal

During 1673 other famous scientists – Gottfried Wilhelm Leibnitz is producing a mechanical calculator which allow easy to be done operation as deducting, multiplying and division. In 1723 the German mathematician and astronomer Kristen Ludwig Gersten uses the base of the Leibnitz work and creates an arithmetic machine.

Around 1820 Charles Xavier Thomas creates the first successful and mass produced mechanical calculator – The Aritmometer of Thomas, with whom you are able to add, multiply, deduct and division. As a rule, the device is based on the work of Leibnitz.

The mechanical calculators which count decimal numbers have been used until 1970.

3.2. 1804: Rising of the aperture cards

In 1804 Joseph Marie Jacquard developed a loom, in which model uses the aperture cards. The series of cards can be replaced, as this replacement of the model does not demand any changes in the mechanic parts of the machine. This is important moment in the history of programming.

Pic. 4. Aperture cards on a music automat (jukebox)

3.3. 1835 – 1900s: first programming machines

The already developed in 1823 machine of Charles Babbage is intended for calculating of mathematical tables, using the principles of programming of Joseph Marie Jacquard.

On the ground of the invention of Babbage and his advises helped on the Swedish inventor Georg Scheutz, to build in 1854 some calculating machines and during 1859 he even sold one to the English Government Agency.

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In 1890 the American Herman Hollerith elaborates an electrical calculating system, which has been used during counting the population of USA between 1890 – 1900. Many computing decisions for the aperture cards are used afterwards until the end of 70es of the past century.

Pic. 5. Differential analyzer, Cambridge, 1938

3.4. Appearance of analogue calculators in the postwar years

Before WWII the mechanical and the electrical analogue computers are the most modern machines and much people believed that this is the future of the computers.

The analogue computers use the advantage from the fact, that the mathematical properties of small size, as a wheel, position, tension, and electricity – are identical as in math, like in the other physical phenomena, ballistic paths, inertia, resonance, carrying of energy, inertia moment and etc. Physical phenomena using values such as voltage and electricity.

3.5. First electro-mechanical digital computers
3.5.1. The first electro-mechanical digital computers – Z series Konrad Zuse

In 1936 the young German engineer Konrad Zuse starts working on his first calculator from Z series, which have a memory and limited programming. During 1938 Konrad Zuse is built his first calculating device called Z series in the apartment of his parents. This is beta model with fully mechanical programming digital computer. The data and command input are doing with the help of a keyboard, and the exit with the help of a little lamp panel. The memory of the counter is organized from the platform of condensers. In the very same year Zuse is approaches to developing of Z2, but his plans are destroyed during the bomb attacks in the WW II.

Pic. 6. Reproduction of the computer Z1 in the museum of the technics, Berlin

The work continues and during 1941 Zuse creates the first calculating machine, which owns all attributes of the modern computer – Z3. It is built on the platform of telephonic relays and works completely satisfactorily. On this way, Z3 is the first working computer. In many

aspects, Z3 is similar like the modern machines, and for the first time it works with calculations consisting a floating comma. The complicated decimal system is replaced with binary, which is more promising and this is one of the reasons which makes Zuse to succeed there, where Babbage cannot. The programs of Z3 are stored on the aperture card. During 90-es is proved and theoretically, that Z3 represent universal computer (if the size on the physical memory is ignored).

The war interrupts the work over the machine. On September 1950 Z4 is finally completed and delivered to ETN Zurich. On this time it is the one computer in Continental Europe and the first in the World, which was sold. It left Mark I with 5 months behind and UNIVAC with ten 10 months behind. The computer works in ETN Zurich until 1955, after that was transferred in the French Aerodynamic Research Institute near Basel, where he worked until 1960.

3.5.2. The British Colossus

During the WW II, Britain has achieved some progress in destroying of encrypted German messages and this is due to the project called "Colossus". The main idea of for the machine is elaborated by Alan Mathison Turing and Gordon Welchman, and the specification for it is worked out by Professor Max Neumann and his colleagues. The assembling of the machine is made in Research laboratory of The Post Department in London and it takes 11 months from the time of Tommy Flowers and Dr. "Colossus" is the first completely digital calculating device, despite is impossible to execute every calculating function.

In Colossus are used a lot of vacuum lamps, and he input data is entered with aperture cards. The machine can be configured on such way to execute different operations on Boolean logic, but this is not a fully Turing's machine. Despite Colossus Mk I, there are other nine models Mk II. The information about the existence of this machine is kept in secret until 1970. Winston Churchill signed by himself the order for destroying the machine to a stage which cannot overpass the size of human hand. Thanks to its secret, Colossus is not mention in many labors of the history of the computers.
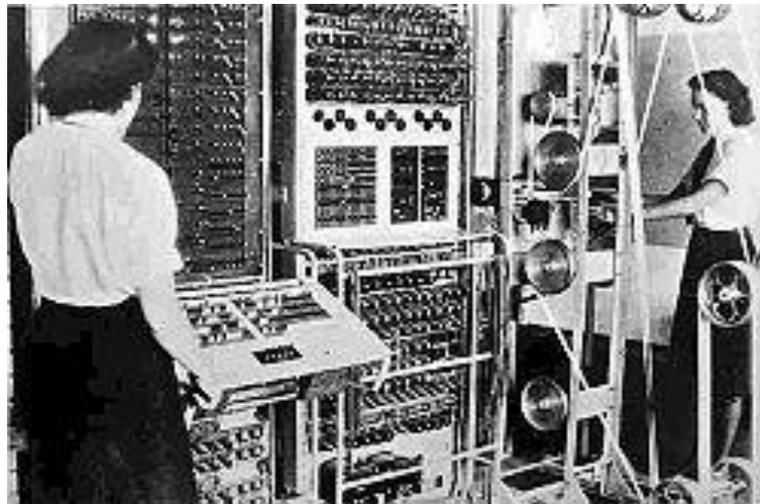
Pic. 7. Colossus

3.5.3. The American treatment

In 1937 Cloth Shannon makes the connection between the conceptions for the Boolean logic and some digital schemes, which now is commonly used in the digital computers. While working in the Massachusetts Technological Institute in the platform of his jobs, he demonstrates that the electronic communication and the keys are part of the Boolean algebra. On November 1937 George Stibitz finalizes computer called "Model K" in Bell Labs, following the relays keys. On 8ᵗʰ of January 1940 is developed Complex Number Calculator, which can execute calculations

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with complex numbers. On 11th September 1940 in Dartmouth College a demonstration made during the conference of American Mathematics Society, Stibitz send remote computer commands, on telephone line from teletype.

Pic. 8. Model K

This is the first case on remote using of computing commands. Among the participants and the witnesses of the demonstration are John Von Neumann, John Mouchli, Norbert Wiener, who writes what they have seen in their memoirs.

The following developing of the computers is connected with the name of John Von Neumann, who in 1945 defines the basic conception for storing the program in the memory of the machine. Principles for building a computer – formulated by John Von Neumann:

➢ The computer is an electronic device which uses a binary code.

➢ The computer works under the control of a program, based on instructions, which are stored in one same linear, one-dimensional and consecutively directed memory.

➢ The memory is directing using numbers of the separate cells without to take in mind the type of the data in them.

➢ There is no clear difference between the data and the instructions of the programs in the memory, the identification of their sturgeon during executing of the programs. The Computer executes the instructions consecutively, after reading the memory.

3.5.4. The Computer Atanasoff-Berry

In 1939 John Vincent Atanasoff and Clifford Berry from the University of the State Iowa developed Atanasoff-Berry Computer (ABC). This is the first electronic digital computer in the World. The construction counts more than 300 electric-vacuum lamps, and the role of memory is taken by a rolling drum. Despite, that the machine ABC was not a programming device, it is the first which uses electric lamps in the adder.

John Vincent Atanasoff is an American physician, mathematician and electric engineer from Bulgarian origin, creator of the first electronic computer.

During the WW II is built the computer ENIAC (Electronic Numerical Integrator and Calculator) with the purpose to calculate ballistic tables for the needs of the American army. Finalized in 1945 from John Mauchly and John Prosper Eckert is believed that this is the first computer until 1973.
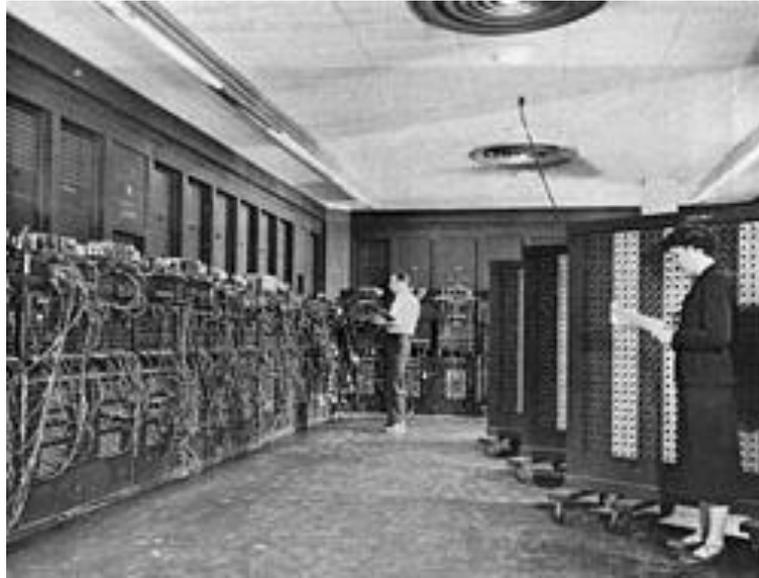
Pic. 9. ENIAC

4. Generations of computers

From the beginning of the 50'es to the end 90'es years the main influence over the developing of the computers causes the level of electronic technics. At this point it can be marked 4 generations of computers:

The First Generation digital computers (1951-1959) are constructed with electronic lamps and works only on machinery language. The control of their calculating process is executing by a human operator.

Second Generation computers (1959-1969) are constructed with transistors, a high level programming languages as (Basic, FORTRAN) are integrated in them.

Third Generation computers (1965-1971) are constructed from integral schemes with low stage of integration. In them there are a lot of innovative decisions for this time – higher level of programming languages (Pascal), the first finalized operation systems (OS), providing the control of the computers with minimal intervention from the human operator's side.

Fourth Generation computers (after 1975), are constructed with huge and enormous integral schemes and microprocessors which allows integrating of microcomputers in such areas, where it was impossible earlier. The modern computers are elaborated on the platform of the universal microprocessors with possibilities for working at the very same time of 32 or 64 ranks binary numbers. Continuously their possibilities are improved.

The Fifth Generation Computer Systems (**FGCS**) was a 10-year initiative begun in 1982 by Japan's Ministry of International Trade and Industry (MITI) to create computers using massively parallel computing and logic programming. It aimed to create an "epoch-making computer" with supercomputer-like performance and to provide a platform for future developments in artificial intelligence. FGCS was ahead of its time, and its excessive ambitions led to commercial failure. However on a theoretical level, the project spurred the development of concurrent logic programming. The term "fifth generation" was intended to convey the system as being advanced: In the history of computing hardware, there were four "generations" of computers. Computers using vacuum tubes were called the first generation; transistors and diodes, the second; integrated circuits, the third; and those using microprocessors, the fourth. Whereas previous computer generations had focused on increasing the number of logic elements in a single CPU, the fifth generation, it was widely believed at the time, would instead turn to massive numbers of CPUs to gain performance.

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Future Generation Computer Systems is a monthly peer-reviewed scientific journal covering all aspects of computer engineering. It is published by Elsevier and the editor-in-chief is Michela Taufer (University of Tennessee). According to the Journal Citation Reports, the journal had a 2019 impact factor of 7.187.[17]

Conclusion

The Informatics is a young subject, which studies the questions, regarding searching, collecting, storing, transforming and using an information in different areas of the human activity. Genetic, the Informatics is connected with the computer sciences, the engineer sciences, the computer systems and networks, because it allows the computers to generate, store, and process the information automatically in such volume, the science approaching of process the information become necessary and possible together.

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INTEGRATIVE THERAPEUTIC METHOD FOR SARS-CoV-2 INFECTION COMBINING FLAVONOID-BASED TRADITIONAL MEDICINE AND SILVER NANOPARTICLES

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Abstract: There are evidences that flavonoids bind to and affect neutrophiles, eosinophils and macrophages. In SARS-CoV-2, the cellular immune response, especially in the first two to three weeks after infection, is expressed by the accumulation at the infection site of at most white blood cell eosinophils, neutrophiles, and monocytes/macrophages.

There have been numerous in *vitro* and *in vivo* studies on the antiviral activity of silver and copper nanoparticles, including in coronavirus infection. The our theoretical idea is that the silver nanoparticles or silver cations are transported by chelation from flavonoids to those white blood cells of the Cell-mediated immunity which are directly involved in the infection.

It was obtained and studied on Covid-19 infection a therapeutic mixture made by a controlled combining of wild basil (*Clinopodium vulgare* L.) tincture (66%, v/v) and other extracts of herbs rich in flavonoid and chlorogenic acid derivatives with a colloidal solution of silver nanoparticles and cations. It was found that the passing of the symptoms typical for the infection is for 3 to 10 days after the start of the treatment course. The highest percentage of patients with passed symptoms was reported from day 4 to day 6 (incl.) after initiation of dosing if therapy was initiated from day 1 to day 4 of the first symptoms. Based on this study, a Utility model "Composition for the treatment of coronaviruses" was registered with the Patent Office of the Republic of Bulgaria.

Keywords: flavonoid chelate complexes, silver nanoparticles, silver cations, SARS-CoV-2, cell-mediated immunity.

Резюме: Съществуват доказателства, че някои флавоноиди се свързват и взаимодействат с неутрофили, еозинофили и макрофаги. При Covid-19 клетъчният имунен отговор, особено през първите две до три седмици след инфекцията, се изразява с натрупване на мястото на инфекцията най-много от белите кръвни клетки еозинофили, неутрофили и моноцити/ макрофаги.

Има многобройни in vitro и in vivo проучвания за антивирусната активност на сребърни и медни наночастици, включително при коронавирусна инфекция. Нашата теоретична идея е, че сребърни наночастици или сребърни катиони се транспортират чрез хелатиране от съединения на флавоноидния ред до онези бели кръвни клетки от клетъчния имунитет, които са пряко участващи в инфекцията.

Беше получена и изследвана при инфекция с SARS-CoV-2 терапевтична смес, направена при контролирано комбиниране на тинктура (66%, v/v) от котешка стъпка (*Clinopodium vulgare* L.) и други екстракти от билки, богати на флавоноиди и производни на хлорогенна киселина, с колоиден разтвор на сребърни наночастици и катиони. Установено е, че преминаването на характерните за инфекцията симптоми е от 3 до 10 дни след началото на курса на лечение. Най-високият процент пациенти с преминали симптоми е отчетен от ден 4 до ден 6 (вкл.) след започване на приема, ако терапията е започнала от първи до четвърти ден след първите симптоми. Въз основа на това проучване в Патентното ведомство на Република България е регистриран полезен модел „Състав за терапия на коронавируси".

Introduction

Following the SARS-CoV pandemic and the efficacy of plant extracts containing large amounts of flavonoids, phenolic acids and other phenols, interest in their potential therapeutic use is focused on the SARS-CoV-2 virus (Russo, Maria *et al*., 2020). Given the impact of the COVID-19 outbreak in China, it was expected that Traditional Chinese Medicine (TCM) could play a major role in the treatment of SARS-CoV-2 infection or at least in alleviating its symptoms. In this regard, by February 22, 2020, along with standard drug treatment, another treatment through TCM against COVID-19 was carried out in China in 60,107 patients. It was found that 92% of those infected with TCM reduced the recovery period by about 2 days, depending on the degree of development of the disease. Patients with mild clinical manifestations were in most cases treated with TCM alone. Only 5% of patients showed worse clinical signs (Publ. Dep. of the People's R. of China, 2020).

The Qingfei Paidu Decoction (QPD) formula is one of the most applied in this national study involving several thousand doctors. As a result of its effective effect, QPD is established as a prescription by the National Health Commission of the Republic of China in the sixth edition of the "Guide to Diagnosis and Therapy in Covid-19". This formula consists of 21 components – herbs and minerals. Its administration showed an effectiveness of 92% in patients at all stages of disease development, including people cured and discharged. And in cases where clinical symptoms have disappeared, people remain stable without deterioration or significant improvement (Yang *et al*., 2020). The beneficial effects of QPD are evident after 6 days of treatment with results of chest computed tomography in which the tracheobronchial shadow is normal, and the inflammation is also suppressed, following the theory and practice of QPD application (Ren *et al*., 2020). In an attempt to identify the main components of QPD and investigate its pharmacological mechanism against COVID-19 infection, Yang *et al.* (2020) applied an integrated multidisciplinary approach – *in silico* method, which includes a pharmacological network and a molecular network of chemical analysis data. The UPLC-MS team identified in QPD 129 compounds grouped into 14 groups, where flavonoids accounted for about 45% of all groups, 15% glycosides, 10% carboxylic acids, 5% saponins and less than 3% terpenoids.

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The action of various representatives of the flavonoid subgroups to suppress the development of viral infection by SARS-CoV 2 may be manifested by various cellular and biochemical mechanisms. One of them is the suppression of enzymes in the coronavirus cycle of infection. One of the main enzymes providing functional (non-structural) components of the virus is thought to be PL [pro] in SARS-CoV 2 and 3CL[pro] in SARS-CoV (Dai *et al.*, 2020). Other significant non-structural proteins of SARS-CoV-2 for its reproducible cycle are RNA-dependent DNA polymerase (RdRp) and helicase (Li and Clercq, 2020). SARS-CoV 2 PL[pro] was found to be significantly inhibited by the flavonoids tomatine A-E (IC50 = 5.0-14.4 μM) (Cho *et al.*, 2013), bavachin, neobavaisoflavone, isobavachalcone, 4′ -O-methylbavachalcone, psoralidin, corylifol A (IC50 = 4.2-38.4 μM) (Kim *et al.*, 2014), quercetin, gallocatechin gallate, epigallocatechin gallate (IC50 = 47-73 μM) (Nguyen *et al.*, 2012), papyriflavonol A (IC50 = 3.7 μM) (Park *et al.*, 2017), Xanthoangelol E (IC50 = 1.2 μM) (Park *et al.*, 2016) and other flavonoid representatives (Russo *et al.*, 2020). NTP-ase/helicase possesses dsDNA looping activity as well as ATPase activity, allowing the helicase to translocate with nucleic acids by hydrolyzing ATP. According to Lee *et al.* (2009) quercetin, at IC50 = 8.1 μM, inhibits SARS-CoV NTP-ase/helicase-based double-stranded DNA looping. And myricitin and scutularin are effective inhibitors of ATP-nitrogenactivity of helicase at IC50 values 2.71 and 0.86 μM, respectively (Yu *et al.,* 2012). Miricitin and several glycosides of quercetin, as well as other phenolic compounds, exhibit both ACE2 and ACEIn inhibitory action (Kumar *et al.*, 2013; Patten *et al.*, 2016; Joshi *et al*, 2020; Khaerunnisa *et al.,* 2020; Antonio *et al.*, 2020)

So far, evidence of inhibition of different stages of the coronavirus cycle of reproduction has been provided. In addition, studies have been carried out on dozens of compounds by *computer* molecular scanning for their potential impact of certain cellular mechanisms in coronavirus infection. TMPRSS-2 is already known to be involved in inoculation and replication of the virus influenza, SARS-CoV, SARS-CoV-2. Through the *in silico* method, several authors have suggested that several flavonoids have the potential to bind to TMPRSS-2, with particular reference to silibin /flavonolignan from milk thistle (*Silybum marianum* L.)/ (Pandit and Latha, 2020) and isogemichalcone B /(e.g. in representatives of the genus breadfruit (*Artocarpus)* / (Rahman *et al.*, 2020).

Theoretical prerequisites for the establishment of the therapeutic approach

Many of the representatives of flavonoids have anti-inflammatory, antihypertensive, antiangiogenic, hepatoprotective, antioxidant, neuroprotective and other actions in humans and animals (Kumar and Pandey, 2013). Particularly effective in viral infections, incl. Influenza A, subtype (H1N1, H5N2, H7N3 and H9N2) (Pantev *et al.*), SARS-CoV (Jo et al., 2020), SARS-CoV-2 (Cherrak *et al.,* 2020; Russo *et al.*, 2020). Respiratory Syncytial Virus, Herpes simplex virus type 1 and 2, etc.[28,29,30] are the subgroups flavonols, flavones, isoflavones, chalcones (Zakaryan *et al.*, 2017; Jo *et al.*, 2020; Zandi *et al.*, 2011).

It is appropriate to present at least some aspects concerning the pharmacokinetics of flavonoids when interacting with certain leukocytes and their involvement in the cellular immune response. In the small and large intestine, flavonoids enter in their glycosidic or aglyconic form. Aglycons passively cross the intestinal barrier, while the transfer of flavonoid glycosides takes place via sodium-glucose-counter transporter-1 (Murota and Terao, 2003). Aglyconic forms were administered orally in native form or converted to such forms by enzymes hydrolyzing and releasing the glycoside residue. These enzymes are excreted by enterocytes and microbial flora in the gut (Murota *et al.*, 2018). In enterocytes or hepatocytes, aglycons are metabolised into glucuronidated, sulphated and/or methylated flavonoids (Day *et al.*, 1998). Glucuronidated forms of flavonoids are the most common representatives of flavonoids in lymphatic flow and blood plasma (Murota *et al.*, 2013). The lymphatic components and the flavonoids merge into the bloodstream through the thoracic canal. Quercetin has been reported to accumulate in rats in their

lungs (Boer *et al*., 2005). There is credible evidence that flavonoids bind to and affect neurophiles (Amirova *et al*., 2019; Tordera *et al*., 1994; Kaneko *et al*., 2017), eosinophils (Weng *et al*., 2008; Middleton, 1998) and macrophages (Mendes *et al*., 2019).

In SARS-CoV 2 (Covid-19), the cellular immune response, especially in the first two to three weeks after infection, is expressed by the accumulation at the infection site of at most white blood cell eosinophils, neutrophils, and monocytes/macrophages (Qin *et al*., 2020; Gómez-Rial *et al*., 2020; Sambataro *et al*., 2020; Baker an Rogge, 2020). Neutralisation of the virus is induced there, as well as inflammatory and other reactions. At the same time, a decrease in the amount of these types of leukocytes is reported in the blood plasma in most cases. (Qin C *et al*., 2020; Gómez-Rial *et al*., 2020). This predominant reduction in blood samples of some types of white blood cells occurs in the majority of cases, and there is often a reduction in the first days after infection of other leukocytes, e.g. basophils.

The mechanism of action of different flavonoids on white blood cells may be different. Metabolic processes (in terms of pharmacodynamics) proposed to reflect flavonoid-mediated immunomodulation of macrophages include a decrease in glycolytic activity observed for all flavonoids tested; increased antioxidant protection; anti-inflammatory reprogramming of the Krebs Cycle (mainly by quercetin); osmotic regulation (by naringin) and membrane modification (by naringenin) (Gómez-Rial *et al*., 2020). It is also essential that several isoflavones bind to macrophage's estrogen receptors (Mendes *et al*., 2019; Kaneko *et al*., 2015) as well as B cells, CD4+ T cells, CD8+ T cells, NK cells, plasma dendritic cells, monocytes and monocyte-derived dendritic cells (Kovats, 2015). The estrogen receptors of macrophage of are characteristic in both women and men (Bhatia *et al*., 2014).

The chemical composition of the herb wild basil (*Clinopodium vulgare L.*) collected in the Rhodope Mountains and/or in the vicinity of the town of Sofia at the stage of butonization – beginning of flowering shows a high content of flavonoids and other phenol compounds (Nikolova, 2011; Dagnon *et al.*, 2018). Flavones, rosmarinic acid, flavonols (Dagnon *et al.*, 2018) add chlorogenic acid (Bardarov, 2016; Amirova, 2019) predominate.

There are also studies that chlorogenic acid derivatives: caffeic acid, rosemary acid, chicoric acid, etc. have antiviral properties against Herpes simplex virus (HSV), Influenza A and immunodeficiency virus (HIV) (Utsunomiya H *et al*., 2014; Langland *et al*., 2018). However, the results of studies reported that the antiviral activity of caffeic acid increased more than 100-fold by adding cations such as Fe^{3+} or anions such as molybdate and phosphate (Langland *et al*., 2018). Tests for cellular toxicity of coffee acid chelates have shown that they have low toxicity. Coffee acid in chelate form with Fe^{3+} has been tested against eight strains of viruses, including from different families. Coffee acid chelates are mostly effective against HSV-1 and HSV-2, but also exhibit moderate activity against Vaccinia virus and VSV-Ebola pseudotyped virus.

Data on the high chelating ability of many subtypes of the flavonoids with metal ions, such as Cu^{2+}, $Fe^{2+,}$ Fe^{3+}, Zn^{2+}, is presented in many sources (Malešev and Kuntic, 2017). These cations are themselves oxidizers. However, most of their chelate complexes with flavonoids have higher antioxidant activity than the same flavonoids that are not bound to cations (Bravo and Anacona, 2001; Mishra *et al*., 2005; Dolatabadi, 2011; Malešev and Kuntic, 2017).

There have been numerous in *vitro* and *in vivo* studies on the antiviral activity of silver (Galdiero *et al*., 2011) and copper nanoparticles, including in coronavirus infection (Jagaran and Singh, 2021; Jeremiah *et al*., 2020).

In addition to metal cations, however, there is also evidence that some flavonoids also form complexes with metal nanoparticles through their free π-electrons and a carbonyl group. Quercetin and centin have the strong chelating ability with copper nanoparticles (Din *et al*., 2017). Quercetin can also bind, cover and stabilize already obtained silver nanochatics (Shujahadeen *et al*., 2019). The same applies to flavonoid-rich flax seed extract (*Linum usitatissimum L.)* (Ajum and Abbasi, 2016; Hussain *et al.,* 2017). and coral vine extract (*Antigonon leptopus*) (Ajum and Abbasi, 2016).

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The aim of this investigation is to obtain and study on Covid-19 infected people the therapeutic mixture obtained by a controlled combination of wild basil tincture and other extracts of herbs rich in flavonoids with a colloidal solution of silver nanoparticles and cations.

Material and Methods

Silver nanoparticles and herb extracts

The silver colloidal solutions as a mixture of NP and cations are obtained by electrolysis and are a product of the company The Colloidal Company, England. The aqueous colloidal solution (25 ppm) is a mixture of silver nanoparticles (NP) and silver cations in a ratio of about 50:50 and is labelled as "silver water". The intake is according to the daily dose specified by the manufacturer, which is 2 times 8 ml per day.

Wild basil (*Clinopodium vulgare* L.) and the herbs contained in the extract with a trade name AI10HERB are collected in the region of Berkovitsa town. The ratio of dry herbs to ethanol-aqueous extractant is 1:10. AI10HERB consists of ethanol-water extract (66%, v/v) from Elderberry (*Sambucus nigra*), White thistle (*Silybum marianum*), Hoary willowherb (*Epilobium parviflorum*), Common nettle (*Urtica dioica*), Medical marsh mallow root (*Althaea Officinalis*), Ginger root (*Zingiber officinale*), Broadleaf plantain (*Plantago major*), Curcuma longa (*Curcuma longa*), Mead wort root (*Filipendula ulmaria*).

Preparation of chelate complexes

To 8 ml of silver water add 20-30 ml of distilled water heated to 60-70 degrees Celsius. Immediately afterwards, 35-39 drops of 66% tincture of Wild basil are added and after 15 minutes of stirring periodically 40-45 drops of tincture AI10HERB of the company Herbalkan Ltd., are added. The described doses are for one intake. Daily intake is two doses.

Treatment study

The two-stage study was conducted: I experimental period (stage) – 20.10-20.12.2020; II experimental period (stage) was additionally conducted because of validation experience – 15.01-28.02.2021.

Stage I: Randomized 37 volunteers in the study group (cohort) and 23 in the control group were enrolled. The effect of the therapeutic method was reported by clinical symptoms characteristic of the virus. An RT-PCR test was performed in all 37 patients and a positive test result was found. Volunteers are between 14 and 65 years old. Except for one participant at 14, the rest are in the range 32-65 years – an average of 43 years. In all participants, the use of this method was started between the first and the fourth day of the first symptoms, with *two or more of the following: fatigue, muscle pain, fever, decreased sense of smell, cough, anaemic-like symptoms*. It is reported on which consecutive day of the beginning of the treatment all the symptoms have passed established at the beginning of the course.

Volunteers between 26 and 63 years were enrolled for the control group – 44.5 years on average. An RT-PCR test was performed in all 23 patients.

Participants from both the control group and the experienced treatment group sought medical examination at the first symptoms, which was predominantly from the Family practice doctors. All subjects were assigned outpatient treatment according to the following model, which was administered equally in the experimental and control groups: zinc glucuronate, selenium methionine, vit. C, vit. D3 and probiotics in the recommended daily doses specified by the manufacturer; also 3 pcs. (1 morning and 2 evenings) Aspirin Protect 100 mg in case the patient does not take other anticoagulants. The patients in the control group who had continued symptoms until day 9, on our recommendation, sought rehabilitation and some of them were hospitalized. Most of the patients in the two consecutive control groups received inpatient treatment according to a treatment protocol from that hospital. We cannot give a specific figure for the number of hospitalized patients. According to the model /protocol/ for therapy presented in this article,

applied in the trial group, only out of hospital treatment under periodic supervision by a doctor has been carried out. There were no fatalities in the experimental or control groups.

Stage II: Randomized 87 volunteers in the trial group and 25 in the control group were enrolled. An RT-PCR test was performed in all patients The experimental group had an age range of 21-73 years (average 47 years) and the control group – 19-68 years (average 43.5 years). Again, in the experimental and control groups, an identical treatment protocol is applied as for Stage I. It is reported on which consecutive day of the beginning of the treatment all the symptoms have passed established at the beginning.

The statistical processing – by student's t-test using SPSS statistics (Kim, 2015) with Ms Office Excel 2010.

Results and Discussion

Passage of the symptoms of the participants in the trial group at experimental period I is for 3 to 9 days after the start of the treatment course. From the data in table 1, the highest percentage of patients with passing symptoms was reported to be from the 4-th to the 6-th day (incl.) after the start of dosing – 70.3% (26 people), and the total for the period from the 3-rd to the 6-th day was about 75% (28 people). On the 7-th and 8-th days without symptoms were 21.6% (8 people) and on the 9-th day – 2.7% (1 person). *For the 10 days of therapy, only a positive effect in terms of the passage of COVID-19 typical symptoms in subjects was reported.*

In the control group, the participants with passed symptoms, except for 2 patients, was between the 13-th and the 26-th from the start of therapy, assigned by the respective attending physician whom they chose to visit. The majority of the symptomatic control group were 17-24 days. A reliable difference of the experimental sleep control variant is reported at $p \leq 0.001$.

Passage of the symptom of the participants in the trial group of the II experimental period is for 4 to 10 days after the start of the treatment course. The data in table 1 reported that the highest percentage of patients with passing symptom was from the 4th to the 6th day (incl.) after the start of dosing – 60.9% (53 people); for the 7th-8th day without symptoms were 33.3% (29 people) and for the 9th-10th day – 5 people. A reliable difference of the experimental sleep control variant is reported at $p \leq 0.001$.

Table 1. Time by number of days from the beginning of the therapeutic course to pass the symptoms characteristic of SARS-CoV-2

	I experimental period		II experimental period	
	Trial Group Participants with resolved symptoms, n=37	**Control group** Participants with resolved symptoms, n=23	**Trial Group** Participants with resolved symptoms, n=87	**Control group** Participants with passed symptoms, n=25
3rd day	2 (5.4%)			
4th - 6th day	26 (70.3%)		53 (60.9%)	
7th - 8th day	8 (21.6%)		29 (33.3%)	
9th - 10th day	1 (2.7%)		5 (5.7%)	1 (4.0%)
11 -16 day		2 (8.7%)		4 (16.0%)
17 - 22 day		15 (65.2%)		13 (52.0%)
23rd - 26th day		6 (26.1%)		7 (28.0%)
Mean day in order from the start of the Symptom Pass, Mean ± SD	*** 5.9 ± 1.25	20.4 ± 3.50	*** 6.4 ± 1.44	19.1 ± 4.34

Legend: p ≤ 0,05 (*); p ≤ 0,01 (* *); p ≤ 0,001 (* * *)*

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Our idea is that the elements effectively acting against the virus silver or copper (whether in the form of nanoparticles or free ions) are transported by chelation from compounds of the flavonoid order to those white blood cells of the cellular immune response that are directly involved in the infection and are in direct interaction with the virus. In addition to the effect, non-metal bound flavonoids have been shown to limit the replication cycle of the virus, as well as anti-inflammatory and other related actions (see introduction). We found that the pH of the mixture tincture of feline step + colloidal water in the given proportion is slightly above 7 and it is suitable for the formation of stable chelate complexes. The rationale for establishing this treatment method for certain aspects of the pharmacokinetics of the administered agents are also presented in this material.

Passage of the symptoms of the subjects in the experimental group at experimental period I is for 3 to 9 days after the start of the treatment course. The highest percentage of patients with resolved symptoms is reported from the 4th to the 6th day (incl.) after the start of the intake – 70.3% and the total for the period from the 3rd to the 6th day is about 75%. In the II experimental period, the passage of the symptoms is for 4 to 10 days, with the highest percentage for the 4th to 6th day after the start of the intake – 60.9%. Our opinion is that the applied mixture according to the author's method gives convincingly good results for claiming that it is suitable for significant assistance in the treatment after Covid-19 infection. The opinion is based on the percentage of infected patients with passed symptoms for the reporting periods compared to a control group.

Conclusions

The mixture obtained by a controlled combination of wild basil tincture and other herb extracts rich in flavonoids, with silver colloidal water, have been shown to improve the healing process in case of SARS-CoV-2 infection.

It was found that the passing of the symptoms typical for the infection is for 3 to 10 days after the start of the treatment course. The highest percentage of patients with passed symptoms was reported from day 4 to day 6 (incl.) after the start of treatment, if the therapy was initiated from day 1 to day 4 of the first symptoms.

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