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Vladimir SKULACHEV
Skulachev Ion (SkQ)
A form of CoQ that is electrophoretically targeted to mitochondria for healing and life extension -- available now

http://en.wikipedia.org/wiki/SkQ
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SkQ

SkQ (10-(6'-Plastoquinonyl)decyltriphenyl-phosphonium) stands for a class of organic molecules composed of a large organic cation (often called "penetrating cation" for the ability to penetrate through lipid bilayer) with antioxidant plastoquinone attached to it. When added to a living cell, penetrating cations are distributed according to the transmembrane electrical potential difference. They traverse across the cell membrane (negatively charged from inside) and accumulate in mitochondria (also negatively charged inside). The concentration of a penetrating cation in mitochondria can be more than 1000-fold higher than its extracellular concentration.

SkQ is a mitochondria-targeted antioxidant

It was proposed that penetrating cations can act as "electric locomotive molecules" and target molecules attached to them in mitochondria.[1] Monitoring the distribution of plastoquinonyl-decyl-rhodamine 19 (SkQR1), a fluorescent SkQ, confirmed that it accumulated almost exclusively in mitochondria. Measurements of mitochondrial reactive oxygen species production revealed that SkQ is a very efficient antioxidant, even when added to the cells in the nanomolar concentration range.

SkQ as a potential anti-aging drug

Production of reactive oxygen species in mitochondria may contribute to senescence. Reactive oxygen species damage mitochondrial DNA and other important cell component, leading to gradual impairment of cellular function. Antioxidants may slow this damage. Several studies indicate that SkQ can efficiently protect the cell from oxidative damage (see [2] for a review).

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http://www.ncbi.nlm.nih.gov/pubmed/19159610
Biochim Biophys Acta. 2009 May; 1787(5):437-61.
doi: 10.1016/j.bbabio.2008.12.008

An attempt to prevent senescence: a mitochondrial approach.

Skulachev VP, et al.

Abstract

Antioxidants specifically addressed to mitochondria have been studied to determine if they can decelerate senescence of organisms. For this purpose, a project has been established with participation of several research groups from Russia and some other countries. This paper summarizes the first results of the project. A new type of compounds (SkQs) comprising plastoquinone (an antioxidant moiety), a penetrating cation, and a decane or pentane linker has been synthesized. Using planar bilayer phospholipid membrane (BLM), we selected SkQ derivatives with the highest permeability, namely plastoquinonyl-decyl-triphenylphosphonium (SkQ1), plastoquinonyl-decyl-rhodamine 19 (SkQR1), and methylplastoquinonyldecyltriphenylphosphonium (SkQ3). Anti- and prooxidant properties of these substances and also of ubiquinonyl-decyl-triphenylphosphonium (MitoQ) were tested in aqueous solution, detergent micelles, liposomes, BLM, isolated mitochondria, and cell cultures. In mitochondria, micromolar cationic quinone derivatives were found to be prooxidants, but at lower (sub-micromolar) concentrations they displayed antioxidant activity that decreases in the series SkQ1=SkQR1>SkQ3>MitoQ. SkQ1 was reduced by mitochondrial respiratory chain, i.e. it is a rechargeable antioxidant. Nanomolar SkQ1 specifically prevented oxidation of mitochondrial cardiolipin. In cell cultures, SkQR1, a fluorescent SkQ derivative, stained only one type of organelles, namely mitochondria. Extremely low concentrations of SkQ1 or SkQR1 arrested H(2)O(2)-induced apoptosis in human fibroblasts and HeLa cells. Higher concentrations of SkQ are required to block necrosis initiated by reactive oxygen species (ROS). In the fungus Podospora anserina, the crustacean Ceriodaphnia affinis, Drosophila, and mice, SkQ1 prolonged lifespan, being especially effective at early and middle stages of aging. In mammals, the effect of SkQs on aging was accompanied by inhibition of development of such age-related diseases and traits as cataract, retinopathy, glaucoma, balding, canities, osteoporosis, involution of the thymus, hypothermia, torpor, peroxidation of lipids and proteins, etc. SkQ1 manifested a strong therapeutic action on some already pronounced retinopathies, in particular, congenital retinal dysplasia. With drops containing 250 nM SkQ1, vision was restored to 67 of 89 animals (dogs, cats, and horses) that became blind because of a retinopathy. Instillation of SkQ1-containing drops prevented the loss of sight in rabbits with experimental uveitis and restored vision to animals that had already become blind. A favorable effect of the same drops was also achieved in experimental glaucoma in rabbits. Moreover, the SkQ1 pretreatment of rats significantly decreased the H(2)O(2) or ischemia-induced arrhythmia of the isolated heart. SkQs strongly reduced the damaged area in myocardial infarction or stroke and prevented the death of animals from kidney ischemia. In p53(-/-) mice, 5 nmol/kgxday SkQ1 decreased the ROS level in the spleen and inhibited appearance of lymphomas to the same degree as million-fold higher concentration of conventional antioxidant NAC. Thus, SkQs look promising as potential tools for treatment of senescence and age-related diseases.

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http://en.skq-project.ru/

Vladimir Skulachev

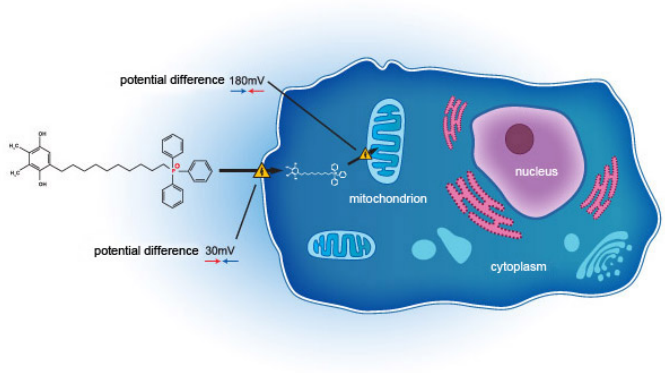
Our project is built around the concept of genetically programmed aging.

Skulachev ions project (or SkQ project) is a coordinated effort to develop a pharmaceutical intervention that would able to slow down or even stop the execution of aging program in human organism. Our goal is to prolong the health span - period of healthy, productive and happy living. There is a lot of data indicating that the process of biological aging is mediated by reactive oxygen species (ROS), generated in the most important cellular organelle – mitochondrion. We based our work on the assumption that a controlled decrease in mitochondrial ROS production may result in deceleration of aging and at the same time may help with treatment of various age-related diseases.

We have created a potent mitochondrially targeted antioxidant SkQ1 to counter excess of mitochondrial ROS and developed several pharmaceutical formulations based on this active compound.

The project is based Moscow State University and operated by the university spin-off company Mitotech. Many laboratories, CROs, clinical hospitals in Russia, US, EU, Australia and other countries participate in the research and development of SkQ-based pharmaceuticals.

Molecule



In 2004, a new substance called SkQ1 was synthesized in the group of professor Vladimir P. Skulachev in the Moscow State University. ” The name SkQ1 was given to the substance as the first representative of a particularly potent class of molecules named “SkQ” – the term introduced by the team to describe molecules containing ion Sk an a quinone.

A part of SkQ1 coined “Skulachev ion” or Sk functions as a molecular “locomotive” or “towing truck” carrying the other part of the molecule – an extremely active antioxidant plastoquinone – into mitochondria. Both theoretical calculations and experimental results showed that SkQ1 is delivered into mitochondria in an extremely targeted and efficient manner. The physics of mitochondrial membrane and the unusual properties of “Skulachev ions” direct SkQ1 into the inner leaflet of the inner mitochondrial membrane with high precision.

Presence of SkQ1 in mitochondrial membrane enables mitochondria to protect itself from reactive oxygen species (ROS) by breaking chain reaction of lipid destruction. This ability of our molecule to protect cells against oxidative stress plays a very important role in treating patients suffering from various age-related disorders such as cardiovascular diseases, neurodegenerative disorders and various ophthalmic conditions.

But our technology does not end there. Developing methods for effective delivery of mitochondrially addressed antioxidants into organism is another challenging task. Mitotech successfully solved this complex problem for a variety of therapeutic areas and designed several SkQ1-based pharmaceutical products going through various stages of clinical development.

Anti-Ageing

It has been hypothesized that age-dependent accumulation of oxidative damages in living organisms may be the main cause of ageing process. It might be possible to control this damage accumulation through controlling the level of ROS production in mitochondria. It is important to stress that ROS production should be controlled, not stopped, so that ROS can still fulfill a number of crucial biological functions. For instance they fight bacteria and viruses, both directly – via elimination of pathogens, – and indirectly – via regulation of the immunological response to infection through triggering apoptosis (cell death).

Antioxidants are a well−developed pharmacological approach to fight against ROS. A possible role of antioxidants in controlling ageing process has widely and for a long time been discussed with ambiguous conclusions, ranging from the statement of the American biochemist Prof. Bruce Ames and colleagues on finding a new anti−ageing therapy with a 100% positive result to D. Howes’s implication of the utter barrenness of this method, and, therefore, of total failure of Harman’s “free radical” hypothesis. According to Dr. Skulachev the antioxidant−based ageing control approach has some significant flaws.

The “ideal” antioxidant should be specifically targeted to mitochondria where ROS are produced and it should effectively remove not all the ROS but just their excess. It is also important for an antioxidant not to be toxic and not to be recognized and eliminated by cell enzymes.

With these criteria fulfilled, a successful anti-oxidant compound should be able to prevent/repair oxidative damage in organism and prevent/treat many age-related disorders across various therapeutic areas.

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http://www.ncbi.nlm.nih.gov/pubmed/20370605
Biochemistry (Mosc). 2010 Mar;75(3):274-80.

Novel mitochondria-targeted antioxidants, "Skulachev-ion" derivatives, accelerate dermal wound healing in animals.

Demianenko IA1, Vasilieva TV, Domnina LV, Dugina VB, Egorov MV, Ivanova OY, Ilinskaya OP, Pletjushkina OY, Popova EN, Sakharov IY, Fedorov AV, Chernyak BV.

Abstract

It is shown that the novel mitochondria-targeted antioxidant SkQ1, (10-(6'-plastoquinonyl) decyltriphenylphosphonium) stimulates healing of full-thickness dermal wounds in mice and rats. Treatment with nanomolar doses of SkQ1 in various formulations accelerated wound cleaning and suppressed neutrophil infiltration at the early (7 h) steps of inflammatory phase. SkQ1 stimulated formation of granulation tissue and increased the content of myofibroblasts in the beginning of regenerative phase of wound healing. Later this effect caused accumulation of collagen fibers. Local treatment with SkQ1 stimulated re-epithelization of the wound. Lifelong treatment of mice with SkQ1 supplemented with drinking water strongly stimulated skin wounds healing in old (28 months) animals. In an in vitro model of wound in human cell cultures, SkQ1 stimulated movement of epitheliocytes and fibroblasts into the "wound". Myofibroblast differentiation of subcutaneous fibroblasts was stimulated by SkQ1. It is suggested that SkQ1 stimulates wound healing by suppression of the negative effects of oxidative stress in the wound and also by induction of differentiation. Restoration of regenerative processes in old animals is consistent with the "rejuvenation" effects of SkQ1, which prevents some gerontological diseases.

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http://link.springer.com/article/10.1134%2FS000629791003003X
Biochemistry (Moscow) March 2010, Volume 75, Issue 3, pp 274-280

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I. A. Demianenko, et al.

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http://www.mitoq.com/

Summary

Mitochondria generate a lot of free radicals so need a constant supply of antioxidants to keep these free radicals in check. MitoQ is an antioxidant that has been formulated to get past the inner mitochondrial membrane to end up deep within the mitochondria. It releases the active form of coenzyme Q10 right at the major site of free radical production, and reduces oxidative stress.

Mitochondria are one of the most important components of a cell. Without them, many crucial biochemical processes would not happen. Not only do they host cellular respiration, the process by which our bodies convert food into energy for the cell, they also send messages to other components within the cell, tailor the cell to perform specific functions, and control both cell growth and cell self-destruction.

Being responsible for so much comes at a cost. Biochemical reactions generate free radicals as by-products. While free radicals do have some important benefits when present in the right numbers, overproduction of free radicals can lead to severe damage of the cell. Unfortunately, over production commonly occurs. Aging, exposure to environmental toxins and pollution and a poor diet can all increase levels of free radicals in our body or cause underproduction of our body's own antioxidants, such as coenzyme Q10 (Co Q10). When free radicals are left unchecked this can lead to oxidative stress.

Which is why developing compounds that target mitochondria makes a lot of sense. Because so many different biochemical processes occur within mitochondria, they generate a lot of free radicals. Mito-Q is a revolutionary mitochondrial-targeted compound that acts directly in mitochondria as an antioxidant against free radicals.

MitoQ is produced by binding a form of Co Q10 called ubiquinone, to a fat soluble, positively-charged molecule. This positively charged molecule is able to flow directly into the mitochondria and through the normally impermeable inner membrane to end up deep inside the mitochondria.

The inside of the mitochondria and inner membrane is the major site for biochemical reactions inside the mitochondria, including cellular respiration. This puts MitoQ exactly where it is needed the most, at concentrations several hundred-fold higher than if it just stayed in the blood. A reaction inside the inner membrane converts the ubiquinone in MitoQ into ubiquinol, the antioxidant and active form of Co Q10. This allows it to neutralise free radicals that accumulate within the mitochondria.

MitoQ is one of the most-studied mitochondrial-targeted antioxidants. Research has shown that after oral administration, MitoQ rapidly accumulates in mitochondria-rich tissue such as the heart, brain, skeletal muscle, liver, and kidney and supports a range of conditions associated with oxidative stress.

You can boost your own natural levels of Co Q10 with MitoQ. When taken alongside a healthy diet and exercise it can reduce damage to your cells inflicted by free radicals.

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http://www.youtube.com/watch?v=etN_eulLO1I
Skulachev project Jan 2013

http://www.youtube.com/watch?v=mZuAo-IhuSQ
Russian scientist anti aging pill - Dr. Skulachev

Bioenergetics (Volume 1787, Issue 5, May 2009, Pages 437–461)
DOI: 10.1016/j.bbabio.2008.12.008

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http://www.mitotechpharma.com/technology

Our Technology

In 2004, a new substance SkQ1 was synthesized by the group of professor Vladimir P. Skulachev in the Moscow State University. A part of SkQ1, coined “Skulachev ion”, functions as a molecular “tow truck” carrying the other part of the molecule – an extremely active antioxidant plastoquinone – into mitochondria. Both theoretical calculations and experimental results showed that SkQ1 is delivered into the mitochondria in an extremely targeted and efficient manner. The physics of the mitochondrial membrane and the unusual properties of “Skulachev ions” direct SkQ1 into the inner leaflet of the inner mitochondrial membrane with high precision.

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http://www.programmed-aging.org/theory-3/skulachev.html

V. P. Skulachev - Programmed Aging Theory

Vladimir Petrovich Skulachev is the chief of the Bioenergetics Department of Moscow State University, dean of the school of Bioengineering and Bioinformatics, and an Academician in the Russian Academy of Sciences, in addition to being director of the MSU Belozersky Institute of Physico-Chemical Biology. He proposed a theory of programmed aging based on evolvability in 1997. His concept, similar to the earlier proposal by Weismann, is that programmed aging assists the evolution process by freeing resources for younger and therefore more evolved members of a population.

Skulachev also suggested that gradual programmed aging, seen in most more complex animals and almost all mammals, has an evolutionary advantage over programmed sudden death seen in some animals such as salmon, octopus, and male marsupial mouse as well as many insects and plants. Unlike "acute" programmed death, gradual aging presents a challenge that can be partially overcome by a more fit individual. This increases the effective difference between a more fit and less fit individual thus aiding the evolution process.

Abstract from Skulachev's Aging is a Specific Biological Function article:

A concept postulating that aging is a specific biological function that promotes the progressive evolution of sexually reproducing species is reviewed. Death caused by aging clears the population of ancestors and frees space for progeny carrying new useful traits. Like any other important function, aging is mediated by several molecular mechanisms working simultaneously. At least three such mechanisms have been postulated thus far: 1) telomere shortening due to suppression of telomerase at early stages of embryogenesis; 2) age-related activation of a mechanism that induces the synthesis of heat shock proteins in response to denaturing stimuli; and 3) incomplete suppression of generation and scavenging of reactive oxygen species (ROS). None of these phenomena can kill the organism, but only weaken it, which becomes crucial under extreme conditions. This mechanism of age-induced death can be compensated for (within certain time limits) by several positive traits that greatly increase the evolutionary potential of species capable of performing this function. Similarly to apoptosis (programmed cell death), the programmed death of the body can be called "phenoptosis". Aging presumably belongs to the category of "soft" (extended in time and allowing a certain degree of compensation) phenoptosis, in contrast to "acute" phenoptosis; the death of salmon females immediately after spawning is a good example of the latter.

Skulachev directs the SkQ Megaproject to study the effect of plastoquinone derivitives (SkQs) in inhibiting oxidation in mitochondria, interrupting the aging program, and consequently providing treatment agents for various age-related conditions. He also conducted a Homo Sapiens Liberatus Workshop in Moscow, May 2010 to review the SkQ results and discuss aging theories. Preliminary results are exciting, especially regarding age-related diseases of the eye.

An incomplete list of Skulachev's publications on programmed aging:

Skulachev V P. Aging is a specific biological function rather than the result of a disorder in complex living systems: biochemical evidence in support of Weismann's hypothesis. Biochemistry. Biokhimiia 1997;62(11):1191-5.
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http://link.springer.com/article/10.1007%2Fs00018-009-9183-6
Cellular and Molecular Life Sciences (June 2009, Volume 66, Issue 11-12, pp 1785-1793)

Functions of mitochondria: from intracellular power stations to mediators of a senescence program

Abstract.

In 1950 s I started in science by showing that non-phosphorylating respiration is critical for survival of an animal at low temperature. Later, in the 1960 s and 1970 s, I took part in verification of Mitchell’s chemiosmotic hypothesis postulating that (i)mitochondria transform energy of respiration to electricity and (ii) uncoupling of respiration represents discharge of this electricity by H+ cycling. Fifteen years ago I turned to a specific kind of mitochondrial respiration which produces O 2 -. , and I came to the conclusion that it plays an ominous role, killing mitochondria, cells, or even organisms. My present task is a “megaproject” with an ambitious goal of minimizing the damaging effect of O 2 -. and stopping senescence.

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http://www.biomedexperts.com/Abstract.bme/9467841/Aging_is_a_specific_biological_function_rather_than_the_result_of_a_disorder_in_complex_living_systems_biochemical_evid
Biochemistry. Biokhimii?a 1997;62(11):1191-5.

Aging is a specific biological function rather than the result of a disorder in complex living systems:

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Vladimir P Skulachev

Abstract

A concept postulating that aging is a specific biological function that promotes the progressive evolution of sexually reproducing species is reviewed. Death caused by aging clears the population of ancestors and frees space for progeny carrying new useful traits. Like any other important function, aging is mediated by several molecular mechanisms working simultaneously. At least three such mechanisms have been postulated thus far: 1) telomere shortening due to suppression of telomerase at early stages of embryogenesis; 2) age-related activation of a mechanism that induces the synthesis of heat shock proteins in response to denaturing stimuli; and 3) incomplete suppression of generation and scavenging of reactive oxygen species (ROS). None of these phenomena can kill the organism, but only weaken it, which becomes crucial under extreme conditions. This mechanism of age-induced death can be compensated for (within certain time limits) by several positive traits that greatly increase the evolutionary potential of species capable of performing this function. Similarly to apoptosis (programmed cell death), the programmed death of the body can be called "phenoptosis". Aging presumably belongs to the category of "soft" (extended in time and allowing a certain degree of compensation) phenoptosis, in contrast to "acute" phenoptosis; the death of salmon females immediately after spawning is a good example of the latter.

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http://www.bioblast.at/index.php/Skulachev_2013_Abstract_MiP2013
Mitochondr Physiol Network 18.08.
Skulachev 2013 Abstract MiP2013

SkQ1, the first mitochondria-targeted medicine available in drugstores

In this group, a concept was put forward considering mitochondrial reactive oxygen species (mtROS) as key intermediates of programmed aging of organism. As a consequence of such a concept, it was suggested that aging program can be retarded (or even switched off) by mitochondria-targeted antioxidants [5]. To this end, 10-(6'-plastoquinonyl) decyltriphenyl phosphonium cation (SkQ1) was synthesized. It was shown that SkQ1 (i) is good penetrant for model and mitochondrial membranes, (ii) has very high affinity to membranes, (iii) is reduced by center i of respiratory Complex III in the inner leaflet of the inner mitochondrial membrane, (vi) electrophoretically accumulates in this leaflet, being driven by the mitochondrial membrane potential, (v) prevents peroxidation of mitochondrial cardiolipin by mtROS, (vi) arrests the ROS-induced apoptosis and necrosis, (vii) prolongs the lifespan of various organisms (from fungi and plants to mammals), and (viii) retards development of many traits of age-related diseases [1-6]. In particular, it was found that drops of SkQ1 instillated to eyes of rats prevent aging of tear glands, an effect leading to cure of such a disease as the dry eye syndrome which is usually assumed to be incurable and can result in uveitis. Clinical trials of drops of 250 nM SkQ1 solution called "Visomitin" showed that the three-week treatment (3 drops per day) completely cure the dry eye syndrome in 60% patients. The following favorable changes were shown: an increase in the amount of tears, stability of tear film, acuity of vision as well as disappearance of inflammation in the eye tissues [7]. Drops of Visomitin are available in drugstores of Moscow and other places of Russia since July, 2012. By May 12, 2013, about 50 000 samples of the SkQ1 drops were sold and no claims concerning an unfavorable side effect were sent to the producers. Clinical trials of Visomitin as potential medicine to treat two other age-related eye diseases, namely cataract and glaucoma, were completed. For one of them (cataract), results are already available. In particular, it was found that acuity of vision was increased in 80.5% cataract patients = 70 years.

Preclinical trials of SkQ1 in treatment of the dry eye syndrome and uveitis were originally performed in Russia and are now confirmed in three laboratories in the USA (Ora Inc., Andover; Toxikon Corp., Minneapolis; Comparative Biosciences Inc., Sunny Vale). In the next future, clinical trials of Visomitin will start in the USA.

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http://instantdane.tv/blog/antioxidant-anti-aging-pill-extends-human-life

A newly discovered antioxidant promises to improve quality of life in the final stage of the human lifespan.

A new breakthrough in longevity science may be well on its way. History has shown that significant scientific advances are often met with skepticism. Such is the case for Russian professor and biochemist, Vladimir Skulachev, as he closes-in on a cure for one of the main factors of aging: oxidative stress.

Though his claims are lofty, he asserts that there is an antioxidant compound that can substantially extend the average human lifespan. His efforts over the past forty years do lend credibility to his claims.

As head of the bioenergetics department at Moscow State University, Professor Skulachev has published numerous papers contributing to our collective understanding of the aging process. More recently he has studied a particular antioxidant substance SKQ1, and shown that it functions at a sub-cellular level to reduce harmful oxidative effects. If successful his current work on a cure for aging would truly be the culmination of a lifetime of study and research.

Skulachev's new anti-aging compound has already undergone substantial animal testing and is now in the first stages of clinical trial on humans. He claims to have successfully tested the anti-aging compound on himself and hopes to make it available to the public within the next two years.

This new antioxidant therapy does not claim to extend the maximum human lifespan. However, it does promise to help more of us live active, vital lives to 100 and beyond.

PATENTS

COMPOSITION FOR DECELERATING THE AGING IN THE ORGANISM AND FOR EXTENDING THE LIFE TIME THEREOF AND THE USE OF SAID COMPOSITION
US2010234326

The invention relates to pharmacology, medicine and gerontology, in particular to a class of chemical structures (1) which can be used in compositions, in the form of geroprotectors, for extending the life time, decelerating, stopping or for reversing the process of the entirety of the organism's dysfunctions causing the mammal ageing and for preventing and treating particular senile diseases.

FIELD OF THE INVENTION

[0001] The invention relates to pharmacology, medicine and gerontology, in particular to a class of chemical structures (I) which can be used in the composition of medicines (preparations) in the fight against various senile diseases, decelerating the ageing, extending the life span of animals including humans.

BACKGROUND OF THE INVENTION

[0002] Nowadays the ageing problem is no longer limited to biological and medical aspects and begins to reach the level of the universal economic problem. In developed countries elderly people are already quantitatively prevail over youth, and the next 25 years the proportion of elderly people in the world will increase by 80% and the proportion of working-age population will decrease accordingly. (Dominguez L. J. Ageing, lifestyle modifications, and cardiovascular disease in developing countries. //J. Nutr. Health Aging, 2006, 10, 2, 143-9). It is obvious that such demographic changes will affect all spheres of life. Mankind will face an acute shortage of resources needed to address the ageing population problems and development issues in general, and therefore the problem of decelerating the human ageing and preventing the development of senile diseases is becoming increasingly important.

[0003] Ageing is a comprehensive and complex process accompanied by dysfunctions in the functioning of critical systems of regulation at the level of the whole organism, at the cellular and molecular levels. Such changes can be observed in various systems of the organism, such as the nervous system (decrease in brain mass, the size and density of neurons, the fall of the bioelectric activity of nerve cells, changes in behavior and learning ability, lipofuscin deposition), the digestive system (e.g., reduction of secretory activity of the digestive organs), the secretory system (reduction of basic renal function), the cardiovascular system (reduction of contractile capacity of the myocardium, increase in systolic blood pressure, slowing of heart rhythmic activity). Also, visual acuity and accommodative power of the eye are reduced, degenerative changes in the retina and cornea are accelerated. There are a slowdown and decrease in protein biosynthesis, increased fat content in various tissues and blood, change in lipid fractions ratio, increase in the frequency of lower tolerance towards carbohydrates and insulin supply to the organism. Degenerative processes in the skeleton (osteoporosis) are accelerated.

[0004] It is generally accepted that the slow poisoning of the organism by toxic oxygen species (ROS) plays a key role in the processes of ageing (V. P. Skulachev (2003) Aging and the programmed death phenomena. In: Topics in Current Genetics, Vol. 3 (T. Nystrom and H. D. Osiewacz, Eds.) Model systems in ageing. Springer-Verlag Berlin Heidelberg, pp. 191-238; V. P. Skulachev (2005) Aging as an atavistic program that we can attempt to cancel. Herald of the Russian Academy of Sciences (in Russian) 75, 831-843). High levels of antioxidants (such as vitamins A and E) in the organism are known to be characteristic of long-livers (Mecocci et al. Plasma antioxidants and longevity: a study on healthy centenarians //Free Radical Biology and Medicine, 2000, 28, 8, 1243-48); on the contrary, genetically determined dysfunctions in the antioxidant systems of the organism lead to accelerated ageing and reduction of the average life expectancy (Liu, J. & Mori A. Age-associated changes in superoxide dismutase activity, thiobarbituric acid reactivity and reduced glutathione level in the brain and liver

in senescence accelerated mice (SAM): A comparison with ddY mice. //Mech. Aging Dev., 1993, 71, 23-30). Attempts to fight against senile diseases, and, ultimately, postpone ageing and death of the organism have been made repeatedly. The approaches used so far to strengthen the antioxidant protection have a positive effect mainly on various ageing-associated diseases, however both average life expectancy and maximum life span usually does not increase (Holloszy J. O. Longevity of exercising male rats: effect of an antioxidant supplemented diet. //Mechanisms of Ageing and Development, 1998, 100, 211-219; Orr, W. C. et al. Effects of overexpression of copper-zinc and manganese superoxide dismutases, catalase, and thioredoxin reductase genes on longevity in Drosophila melanogaster. //J Biol Chem., 200, 3 278 (29), 26418-26422). The data on antioxidant-induced extension of life span in the organisms with pathologically accelerated ageing, relative to normal members of their species, are the exception. For example, antioxidants can increase the average life expectancy of mice in a state of permanent oxidative stress due to dysfunctions in the ATM gene (Reliene R. & Schiestl R. Antioxidants Suppress Lymphoma and Increase Longevity in Atm-Deficient Mice //The Journal of Nutrition, 2007, 37, 229S-232S). According to the theory implying that ageing is part of the program(s) of the individual organism's development, low efficiency of the antioxidants used so far can be accounted for by organism's intention to fulfill the ageing program encoded in its genome despite our attempts to stop it. Indeed, the introduction of large doses of vitamin E appeared to induce the cytochrome P450 enzyme in liver microsomes which removes the excess antioxidant (Y. A. Sidorova, A. Y. Grishanova, V. V. Lyakhovich (2004). Transcriptional activation of cytochrome P450 1A1 with alpha-tocopherol. Bull Exp Biol Med., 138(3), 233-6.). Apart from the susceptibility to antioxidant-scavenging enzymes in the organism, traditional antioxidants have a disadvantage that they are uniformly distributed throughout the cell volume, rather than accumulate in the mitochondria responsible for generating the bulk of ROS in the organism.

[0005] Many known remedies increase the average life expectancy (ALE) of animals and humans. However the maximum life span (MLS) is not increased which implies that these remedies are aimed at correcting the pathological consequences of ageing, rather than the fundamental processes of ageing. Thus, mankind has almost exhausted the possibilities of extending the life span by traditional medicines, and in the first place there is a problem of developing means and methods of a radical impact on the ageing process. In this case, the term "the fight against ageing" implies decelerating, stopping or reversing the process of the entirety of the organism's dysfunctions causing the ageing, extending the life time, prevention or correction of dysfunctions that accompany the ageing process, in order to increase the length of productive life, and postpone these senile dysfunctions to a later date (or even cancel them).

[0006] The assumption of the possible effect of increasing life span and decelerating ageing induced by described compounds of structure (1) was also made in the patent application of the author of the given invention registered under the number RU 2005132217 dated Oct. 19, 2005. However, the experimental examples shown in the given patent application are only vaguely related to both the problem of extending the life time in general and specific senile diseases, and do not allow to state the usefulness of compounds of structure (1) in the fight against ageing as such.

DESCRIPTION OF THE INVENTION

[0007] The present invention suggests not only a theoretical possibility of the fight against ageing, but also a specific method based on the use of a set of compounds specifically addressed to the mitochondria by virtue of their positive charge. This charge is shielded by hydrophobic substituents that endows the compounds with the ability to penetrate through biological membranes without the aid of any carriers under the influence of electrical potential difference that is always available in the mitochondrion (the sign "minus"-inside the mitochondrion). The invention provides not only a potential ability for the fight against ageing with the use of said compounds, but also specific compositions, modes and procedures of their application for the fight against ageing.

[0008] One aspect of the present invention is a new application of a pharmaceutical composition of cationic antioxidants to produce medicinal preparations that are intended for the prevention and treatment of various pathologies of ageing and extending the productive life time. Said composition comprises compounds that include targeting moiety, linker group and antioxidant, and the general chemical structure of these compounds can be described by the following structure (I):

[0009] wherein A is effector moiety-antioxidant

[0000] and/or reduced form thereof
wherein m is an integer from 1 to 3; each Y is independently selected from the group consisting of: lower alkyl, lower alkoxy; or two adjacent Y groups, together with carbon atoms to which they are attached, form a following structure:

[0010] and/or reduced form thereof

wherein R1 and R2 may be the same or different and are each independently lower alkyl or lower alkoxy;
L-linker group, comprising:
a) straight or branched hydrocarbon chain which can be optionally substituted by one or more substituents and optionally contains one or more double or triple bonds;
b) natural isoprene chain;
n is integer from 1 to 20;
B-targeting group comprising Skulachev-ion Sk:

[0000]
Sk<+>Z"

where Sk-lipophilic cation, Z-pharmacologically acceptable anion; with proviso that in compound of structure (I) A is not ubiquinone (e.g., 2-methyl-4,5-dimethoxy-3,6-dioxo-1,4-cyclohexadienyl) or tocopherol or mimetic of superoxide dismutase or ebselen; while L-divalent decyl or divalent pentyl or divalent propyl radical; and while B is triphenylphosphonium cation; or solvates, isomers and prodrugs; and pharmaceutically acceptable carrier thereof.

[0018] Another aspect of the present invention is the use of a pharmaceutical composition for manufacturing medicinal preparations that are intended for extending the life time of humans and animals, as well as for prevention and treatment of senile diseases, such as retinal dystrophy, cataract, uveitis, glaucoma, cardiac infarction, renal infarction, stroke, diabetes, trophic ulcers, mental disorders, anemia, osteoporosis, cancer, etc.

[0019] One more aspect of the present invention is a pattern of use (treatment course) suggesting the use of high doses of a preparation comprising a compound of structure (I), in the treatment of older patients, as well as a gradual increase in dosage preparation comprising a compound of structure (I), with increasing age of individual patient. Such procedure is intended to compensate for age-related reduction of natural antioxidant protection of the organism with ageing. Acceptable doses for oral administration are from 1 nanogram to 100 microgram per kg of patient body weight, 60 nanogram per kg of body weight of patients aged from birth to 10 years is more preferable; from 1 nanogram to 500 microgram per kg of patient body weight, 600 nanogram per kg of body weight of patients aged 10 to 25 years is more preferable; from 5 nanogram to 1000 microgram per kg of patient body weight, 3 microgram per kg of body weight of patients aged 25 to 40 years is more preferable; from 10 nanogram to 10000 microgram per kg of patient body weight, 30 microgram per kg of body weight of patients aged 40 years and older is more preferable.

[0020] In the present invention, the wording "extending the life span" means extending the life span that can be achieved by decelerating the ageing, decelerating or reversing the age-dependent changes in the organism. Without wishing to be bound by any theory, solely to illustrate the possibility of implementing the present invention, a possible theoretical justification that mitochondria-addressed compounds of structure (I) may affect the ageing process is given below.

[0021] The said justification is based on the theory of programmed death of the organism (phenoptosis) (V. D. Longo, J. Mitteldorf and V. P. Skulachev (2005) Programmed and altruistic ageing. Nature Review Genetics 6, 866-872). According to this theory, in a large number of cases, the reason of "age-induced" death of the organism is not because the organism "exhausted its own resource", but is due to the action of the program encoded in this organism that specifically and actively limits its life span.

[0022] In nature, many cases of programmed death of the organism have been described, and for different species this program can be implemented in different ways. However, the scientific data available (see Background of the invention) suggest that ROS formed in the mitochondria play an important role in implementing this program. Hence, compounds of structure (I) may affect the said program.

[0023] Application of pharmaceutical compositions relating to the present invention can be both somatic and local. Procedures of administration comprise enteral, such as oral, sublingual and rectal; local, such as transdermal, intradermal and oculodermal; and parenteral. Suitable parenteral procedures of administration comprise injections, for example, intravenous, intramuscular, subdermal, intraperitoneal, intra-arterial, and other injections, and non-injecting practices, such as vaginal or nasal. Preferably, compounds and pharmaceutical compositions related to the present invention, are for parenteral or oral administration. In particular, administration can be given in form of intravenous injections or tablets, granules, capsules or other pressed or compressed form.

[0024] When a compound of structure (I) is administered as a pharmaceutical composition, a compound of structure (I) should be mixed according to formula with a suitable amount of pharmacologically acceptable solvent or carrier so that to have the appropriate form for administration to a patient. The term "solvent" relates to diluent, auxiliary medicinal substance, filler or carrier which is mixed with a compound of structure (I) for administration to a patient. Liquors like water, and oils including petrolic, animal, vegetative and synthetic, such as peanut oil, soybean oil, mineral oil and other similar oils can be used as said pharmacological carriers. Normal saline solution, acacia pitch, gelatin, starch, talc, keratin, colloid silver, urea etc can serve as said pharmacological solvents.

[0025] Said composition can also include auxiliary substances, stabilizers, thickeners, lubricant and coloring agents.

[0026] Compounds and compositions related to the present invention can be administered in form of capsules, tablets, pills, pillets, granules, syrups, elixirs, solutions, suspensions, emulsions, suppositories or retarded release substances, or in any other form suitable for administration to a patient. One aspect of the present invention is application of compounds of

structure (I) and compositions in form of solutions for oral and parenteral administration.

[0027] Therapeutically justified amount of a compound of structure (I) required for treatment of a specific disease or symptom, depends on the nature of disease or symptom and a procedure of administration and should be determined at consultation with a physician in charge. Acceptable doses for oral administration are from 0.025 to 120000 microgram per kg of patient body weight, 1.5 microgram per kg of patient body weight is more preferable, and 3 microgram per kg of patient body weight is the most preferable. Acceptable doses for intravenous administration are from 0.001 to 10000 microgram per kg of patient body weight, 0.01 microgram per kg of patient body weight is more preferable, and 0.1 microgram per kg of patient body weight is the most preferable.

[0028] Examples of Acceptable Pharmaceutical Compositions for Oral Administration:

Pharmaceutical Composition-1-Gelatin Capsules:

[0029]

Ingredient	Amount (mg/capsule)
Compound of structure (I)	0.0015-1000
Starch	0-650
Starch powder	0-650
Liquid silicone	0-15

Pharmaceutical Composition-2-Tablets:

[0030]

Ingredient	Amount (mg/capsule
Compound of structure (I)	0.0015-1000
Microcrystalline cellulose	200-650
Silicon dioxide powder	10-650
Stearic acid	5-15

Pharmaceutical Composition-3-Tablets:

[0031]

Ingredient	Amount (mg/capsule)
Compound of structure (I)	0.0015-1000
Starch	45
Microcrystalline cellulose	35
Polyvinylpyrrolidone (10% aqueous solution)	4
Carboxymethylcellulose, sodium salt	4.5
Talc	1
Magnesium stearate	0.5

Pharmaceutical Composition-4-Suspensions:

[0032]

Ingredient	Amount (mg/5 ml)
Compound of structure (I)	0.0015-1000
Syrup	1.25
Benzoic acid solution	0.10
Carboxymethylcellulose, sodium salt	50
Flavoring	By necessity
Coloring	By necessity
Distilled water	Up to 5 ml

An Example of Acceptable Pharmaceutical Composition for Administration in the Form of Aerosol:

[0033]

Ingredient	Amount (weight percent)
Compound of structure (I)	0.0025
Ethanol	25.75
Difluorochloromethane	70

An Example of Acceptable Pharmaceutical Composition for Administration in the Form of Suppositories:

[0034]

Ingredient	Amount (mg/suppository)
Compound of structure (I)	1
Glycerides of saturated fatty acids	2000

An Example of Acceptable Pharmaceutical Composition in the Form of Solution for Intravenous Administration (pH 6.5):

[0035]

Ingredient	Amount
Compound of structure (I)	5 mg
Isotonic solution	1000 ml

BRIEF DESCRIPTION OF FIGURES

[0036] FIG. 1 demonstrates the effect of the preparation on life span of SHR mice. (The figure shows a survival curve for SHR mice daily received SkQ1 with water).

[0037] FIG. 2 shows the data demonstrating the effect of the preparation on life span of D. melanogaster flies. (The figure shows a survival curve for D. melanogaster flies daily received SkQ1 with food).

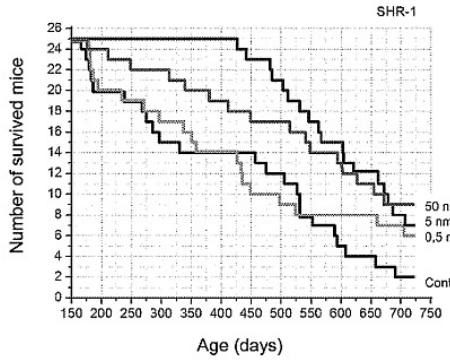
[0038] FIG. 3 demonstrates the effect of the preparation on life span of p53 (-/-) transgenic mice lacking the p53 gene. (The figure shows a survival curve for mice lacking the p53 gene daily received SkQ1 with water).

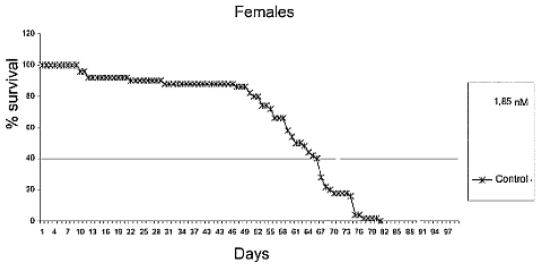
[0039] FIG. 4 shows the effect of SkQ1 on the mass of bone tissue of OXYS rats as a result of administering SkQ1.

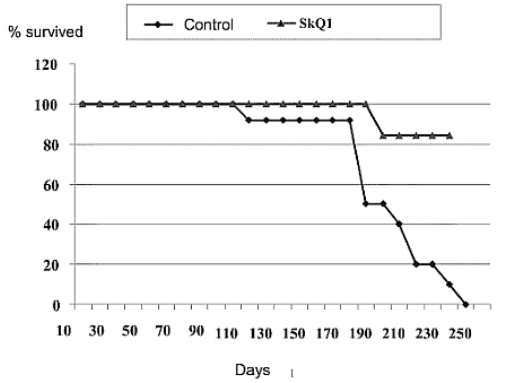
[0040] FIG. 5 shows data on the preparation-induced changes in bone mineral density of Wistar and OXYS rats. (The figure shows changes in bone mineral density (hip) as a result of administering SkQ1).

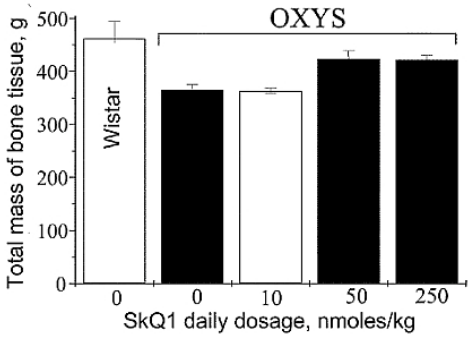
[0041] FIG. 6 shows the results of the long-term course of administering the preparation on the extent of sexual motivational behavior in male OXYS rats. (The figure shows the effect of administering SkQ1 on time spent by a male rat near a female rat separated by a barrier inserted between the rats (a parameter characterizing male sexual motivation)).

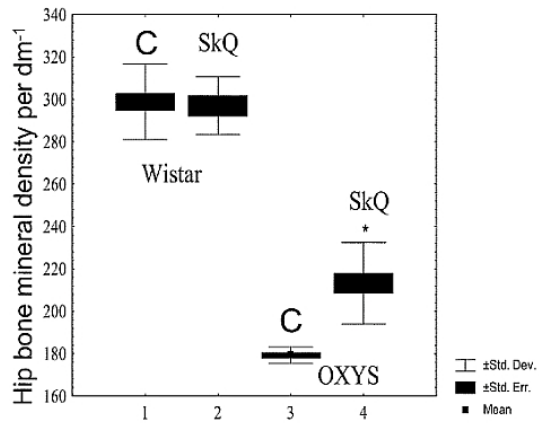
[0042] FIG. 7 shows data on a prophylactic effect of SkQ1 on age-related dysfunctions of memory and learning ability (the Morris maze test) in OXYS rats. (The figure shows the effect of administering SkQ1 on time spent by rats to find the platform under water in the Morris maze (test of learning ability)).

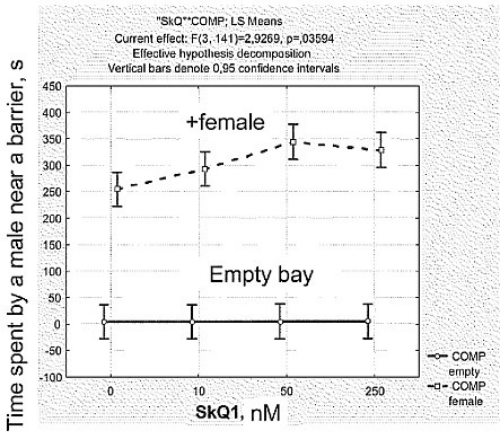


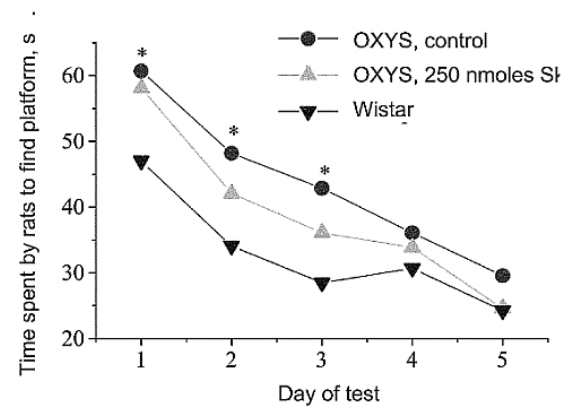












[0043] The following non-limiting Examples illustrate the preparation and use of compounds of structure I but should not be understood as limiting the invention as modifications in materials and methods will be apparent to the skilled person. The following examples should not be construed as limiting the scope of this disclosure. Apart from extending the actual life span, these examples show that the correct use of compositions based on compounds of structure (I) can extend the live time of animals, decelerate and in some cases reverse the development of several independent signs of ageing.

EXAMPLES

1. Increase of Life Span in SHR Mice by Means of Mitochondria-Targeted SkQ1 Antioxidant

[0044] An experiment with outbred SHR mice was carried out. The mice were divided into four groups (25 animals per each group). The three groups received a certain amount of SkQ1 with drinking water throughout their lives, and the fourth (control) group received water without SkQ1. Data on the time of animal deaths in all groups are shown in FIG. 1. Dose of SkQ1 is given in nanomoles per kg of animal weight per day.

[0045] The data shown in the Figure conclusively demonstrate the ability of SkQ1 to extend the life span of SHR mice which are a generally accepted model for gerontological studies. (V. N. Anisimov, I. N. Alimova, D. A. Baturin, I. G. Popovich, M. A. Zabezhinski, S. V. Rosenfeld, K. G. Manton, A. V. Semenchenko, A. I. Yashin (2003) Dose-dependent effect of

melatonin on life span and spontaneous tumor incidence in female SHR mice. Exp Gerontol. 38, 449-461). Indeed, mice that received SkQ1 in optimal doses (1 nanomole per animal per day) revealed much longer life span: in 707 days of the experiment, in the control group, 8% of the animals remained alive, while in the test group-36%, 28% and 24%, respectively.

[0046] The same experiment showed that female SHR mice received SkQ1 are characterized by less pronounced age-related changes in estrous function, as compared to the control group. With increasing the duration of the observation period, tendency of decelerating age-related disorders in estrous function in experimental animals becomes more pronounced, which were expressed as increase in the duration of cycle and lowering the frequency of regular cycles. For example, in the 2<nd >cohort in 15-month-old experimental animals received SkQ1 at a dose of 0.01 nanomoles per day, the frequency of regular cycles was 94%, whereas in the control-67%. These data suggest decelerating age-related disorders in estrous function in SHR mice under the influence of SkQ1.

2. Increase of Life Span in Female Fruit Flies (Drosophila melanogaster) by Means of SkQ1

[0047] Isogenous laboratory Drosophila line w<1118 >in which all individuals have the same genotype was chosen for the experiments, thus eliminating the influence of genetic differences between individuals on the results of experiments. The mitochondria-targeted antioxidant SkQ1 at a concentration of 1.85 nM was tested. Stock SkQ solution was diluted in distilled water. Adult flies were administered the compound throughout their lives. Since adult flies can feed on food located on the surface, it was decided to spread the SkQ1 solution of a corresponding concentration on the surface of freshly prepared medium poured into test tubes containing the flies.

[0048] Virgin females and males of line w<1118 >selected during the day were placed in tubes, each tube contained five individuals (males and females separately), in standard medium. In control tubes, 100 [mu]l of distilled water without SkQ was spread on standard medium surface; in test tubes, 100 [mu]l of the test compound at a selected concentration was spread on standard medium surface. The number of live flies in each tube was recorded daily, once a week flies were transferred to a corresponding fresh medium. All tubes were incubated at 25[deg.] C. In each experiment, 100 individuals (20 tubes) were analyzed.

[0049] Analysis of the survival curves for flies showed that SkQ1 at a concentration of 1.85 nM resulted in reliable increase of the average life expectancy from 58 to 66 days (P=0.0012). A fraction of individuals aged 70 days and older in the group received feed with 1.85 nM SkQ1 is reliably higher than that in the control group (0.48 and 0.18, respectively, P=0.0056). The survival curves for flies are shown in FIG. 2.

[0050] The results of this experiment indicate that the mitochondrial antioxidant of SkQ1-type increases the life span of flies D. melanogaster.

3. Increase of Life Span in p53 Gene Knockout Mice

[0051] Mice lacking the p53 gene (p53-/-) can not synthesize the p53 protein, so-called "guardian of the genome", and can serve as a model of accelerated ageing and death of the organism caused by cancer [for more details, see A. A. Sablina, A. V. Budanov, G. V. Ilyinskaya, L. S. Agapova, J. E. Kravchenko, P. M. Chumakov (2005) The antioxidant function of the p53 tumor suppressor //Nature Med., 11, 1306-1313)]. Within the framework of the aforementioned theory of phenoptosis implying the key role of mitochondrial reactive oxygen species in organism's aging, one may suggest that compounds of structure (I) can significantly extend the life span of p53 (-/-) mice. This example demonstrates the results of such experiment.

[0052] Based on the previously conducted PCR analysis detecting p53-/-, p53+/- and p53+/+ mice in the progeny of heterozygous (p53+/-) animals, the two groups of mice were drawn up which received:

clean drinking water;
water supplemented with SkQ1 (0.1 nmoles of the preparation per mouse per day (5 nM/kg/day)).

[0055] The experimental results are shown in FIG. 3.

[0056] The experimental curves clearly show a dramatic increase of the life span in animals received SkQ1 with drinking water.

4. Reversing a Sign of Ageing

Senile Blindness in Pets

[0057] In support of the possibility of execution of the invention, this experimental example shows several protocols for clinical trials of pharmaceutical compositions based on compounds of structure (I) as a veterinary preparation.

[0058] A) Patient-cat, breed-European Shorthair, age-15 years. Diagnosis-retinitis, papillitis, senile generalized progressive retinal dystrophy. Clinical signs-depigmentation of t. lucidum, the optic disk (OD) is violet. Retinal detachment. Vision is absent.

[0059] Treatment-daily instillation of 250 nM SkQ1 solution (in physiological solution at pH 6.5).

[0060] Results-after 10 days of the treatment the pupil began to respond to light, the cat began to play with the ball and see even small objects. In the study of eye fundus, only pinpoint hemorrhages were identified. Retinal detachment and dystrophy areas are absent. OD became pink. After 21 days of the treatment-vision retained; retinal detachment and dystrophy areas are absent. OD is pink.

[0061] B) Patient-horse, gelding, not thoroughbred, age-20 years. Diagnosis-senile blindness associated with degeneration of the retina and its vessels. Clinical signs-shortening and thinning of retinal vessels emanating from the optic disk, depigmentation of t. lucidum t. nigrum, thinning of the retina over the entire surface of eye fundus. As a result, Choroid blood vessels in the form of straight lines are well visualized, posterior polar senile cataract is detected. The animal cannot see during the last eight months.

[0062] Treatment-daily instillation of 250 nM SkQ1 solution (in physiological solution at pH 6.5), and since the 3<rd >month of treatment-2 times a day.

[0063] Results after 90 days of the treatment-original color of t. lucidum returned, old vessels emanating from OD are filled with blood, highly convoluted, short. OD is pink. The growth of 40 new blood vessels from OD was detected. The vessels are long, filled with blood (similar to foal's vessels). The vision was restored in the animal.

5. Preventing the Development of a Sign of Ageing

Age-Dependent Decrease in Bone Mass (Osteoporosis) in Rats

[0064] Osteoporosis is one of the most common senile diseases manifesting itself as bone thinning and increase in bone fragility. Today, this disease has become so commonplace that it can be referred to as a quiet epidemic. In osteoporosis, entire sections of bone tissue disappear, bone loses its complex architecture. Traditional antioxidants are ineffective for osteoporosis prevention (Wolf R. L. et. al. Lack of a relation between vitamin and mineral antioxidants and bone mineral density: results from the Women's Health Initiative //American Journal of Clinical Nutrition, 2005, 82, 3, 581-588). The next series of experiments demonstrates the possibility of preventing the development of the main symptom of osteoporosis-reduced bone mineral density.

[0065] Experiments were conducted on the two lines of rats-Wistar and OXYS. Genetically determined metabolic defect, manifesting itself as decreased resistance of OXYS rats towards oxidative stress, leads to changes in their organism which may be regarded as accelerated ageing syndrome. In particular, reduced bone mineral density in OXYS rats, as compared to Wistar rats, is observed. Such changes are also observed in osteoporosis in humans that allows us to consider these animals as an adequate model of senile osteoporosis in humans.

[0066] Wistar and OXYS rats, -control rats and those who received two courses of SkQ1 (50 nanomoles per kg of body weight per day), were studied. The animals received the preparation since 1.5 and 4 months of age for 45 days. At the age of 6 months, bone tissue state was studied by X-ray densitometry.

[0067] It was shown that, in OXYS rats, the preparation reliably increased bone mineral density of femur and tibia (FIG. 4) and the total mass of bone tissue (FIG. 5). Thus, the preparation reduces the severity of osteoporosis in OXYS rats.

6. Preventing the Development of a Sign of Ageing

Age-Dependent Reduction of Sexual Motivation in Rats

[0068] It is known that ageing in higher organisms is often accompanied by weakening of reproductive instincts and reduced sexual motivation. The next series of experiments demonstrates the possibility of preventing the development of such behavioral disorders with the previously mentioned Wistar and OXYS rats as an example.

[0069] Both at the age of 3 months and at one year Wistar males show considerable interest in females. In the study of sexual motivation in OXYS rats at different age periods, somewhat different results were obtained. One year old OXYS males show less interest in females, as compared to OXYS males at the age of 3 months.

[0070] The effect of monthly course of SkQ1 (50 nanomoles per day) on the extent of sexual arousal in one year old Wistar and OXYS males was investigated. To do this, an experimental model of sexual arousal was used-males were kept under conditions allowing them to see the receptive female, perceive the female's smell, but excluding physical contact with the female. Under these conditions, male rats and male mice show increase in blood testosterone level and typical motivational behavior.

[0071] It was shown that under the influence of SkQ1, interlinear differences between Wistar and OXYS rats by the main behavioral indicator of sexual arousal, -time spent by a male rat near a female rat separated by a barrier inserted between the rats, disappeared. SkQ1 reliably increased this indicator in OXYS rats administered 50 and 250 nanomoles of SkQ1 (as compared to the values for sexual arousal in the control (no SkQ1 was given) males (FIG. 6). Thus, long-term SkQ1 administration enhanced the sexual motivation of OXYS male rats with a genetic predisposition to premature ageing, bringing it to the level shown by Wistar male rats with a normal rate of ageing.

7. The Effect of Long-Term SkQ1 Administration on "Investigatory Reflex" and the Ability of Animals to Learn

[0072] The next series of experiments reveals SkQ1 ability to decelerate the development of age-related changes in learning ability, using Wistar and OXYS rats as an example.

[0073] The Morris water maze test is actively used for studies on learning and long-term spatial memory in animals. The method of Morris allows to evaluate strategies for behavior, dynamics of skill formation, to detect even weak differences in behavior. This test evaluates the ability of an animal, swimming in the opaque water of the pool and looking at the signs on its sides, to learn how to find the invisible, hidden platform under water, no matter from what point of the perimeter of the pool the animal was released. Progress in passing spatial orientation tests depends on the function of the hippocampus, and, in the development of senile neurodegenerative processes, this function is significantly reduced. Preliminary experiments showed that Wistar rats at the age of 3, 12 and 16 months do not differ in their ability to learn in the Morris maze, whereas in OXYS rats such ability decreases with age.

[0074] In subsequent experiments, 4 groups of 16-month-old animals: control Wistar and OXYS rats, and groups received the preparation since 1.5 months at a dose of 250 nanomoles per kg of body weight, were used. A latent period of time spent by rats to find the platform depended only on the genotype-it took longer in OXYS rats than in Wistar rats-OXYS rats coped worse with the task. Under the influence of SkQ1, interlinear differences between Wistar and OXYS rats disappeared-SkQ1 improved the ability of OXYS rats to learn (FIG. 7).

[0075] Thus, it was shown that prophylactic administration of the preparation SkQ1 has a positive effect on memory and prevents age-related decline in the ability to learn in the Morris maze in OXYS rats.

[0076] A further series of behavioral tests "open field" and "elevated cruciform maze" demonstrated a positive effect of SkQ1 on search and exploratory activity of rats. In addition, a clear stress-protective effect of SkQ1 administration was observed with Wistar rats.

PHARMACEUTICAL COMPOSITIONS FOR PREVENTING AND TREATING EYE PATHOLOGIES
US8658624 // WO2008048134

The present invention relates to pharmacology, medicine, ophthalmology, and, in particular, concerns a class of chemical compounds of structure (I) and also their solvates, isomers or prodrugs applicable when incorporated into pharmaceutical compositions also containing pharmaceutically acceptable carrier which can be useful for prophylaxis and treatment of different eye pathologies such as cataract and macular dystrophy.

ORAL FORMULATIONS OF MITOCHONDRIALLY-TARGETED ANTIOXIDANTS AND THEIR PREPARATION AND USE
WO2012167236

Provided are stable liquid and solid formulations of oxidized and reduced mitochondria-targeted antioxidants, and methods of their preparation and use.

USE OF MITOCHONDRIALLY-ADDRESSED COMPOUNDS FOR PREVENTING AND TREATING CARDIOVASCULAR DISEASES
US2013338115

The invention relates to pharmacology and medicine, in particular to a class of mitochondrially-addressed compounds which can be used in the pharmaceutical compositions of medicinal agents (preparations) for preventing and treating cardiovascular diseases and diseases and pathological conditions caused by disturbed blood circulation or oxygen supply to tissues and organs.

PHARMACEUTICAL COMPOSITION FOR USE IN MEDICAL AND VETERINARY OPHTHALMOLOGY
US2012094962 // WO2010143990

The invention relates to pharmaceutics, medicine, in particular to manufacturing and use of pharmaceutical compositions of medicines (ophthalmic preparations) comprising mitochondria-addressed antioxidant and a set of auxiliary substances providing effective treatment for ophtalmological diseases in humans and animals.

MILD CATIONIC MITOCHONDRIAL UNCOUPLERS
US2013203843

The present invention relates to biology and medicine and in particular can be used in medicine for the preparation of a pharmaceutical composition for the specific, self-regulating uncoupling of mitochondria. The invention can be useful in the treatment of diseases and conditions associated with the disruption of cellular metabolism, in the treatment of obesity, including pathological forms thereof, and also for the treatment of diseases associated with the increased formation of free radicals and reactive oxygen species.

PHARMACEUTICAL SUBSTANCES ON THE BASIS OF MITOCHONDRIALLY ADDRESSED ANTIOXIDANTS.
US2012259110 // WO2011059355

This invention relates to the fields of pharmaceutics and medicine, and, in particular, concerns the production and use of pharmaceutical substances on the basis of mitochondrially addressed compounds. The invention discloses methods for synthesizing, cleaning and storing mitochondrially addressed antioxidants, making it possible to produce said substances in a form and quality meeting the demands made on active substances of medicinal preparations - the pharmaceutical substances. The invention also discloses methods for making and selecting novel mitochondrially addressed antioxidants having specified properties.

PHARMACEUTICAL COMPOSITIONS USEFUL FOR PREVENTING AND TREATING CANCER
US2013072463

Disclosed is a method of treating a cancer on a mammal, comprising administering to the mammal in need thereof a therapeutically effective amount of a compound

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MITOCHONDRIA-TARGETED ANTIOXIDANTS FOR TREATMENT OF AGE-RELATED BRAIN DISORDERS
WO2013044058

A method for providing to a mammal a neuroprotective effect against a brain pathology that is associated with reactive oxygen species originating from mitochondria (mROS). The method includes the step of administering to the mammal an SkQ mitochondria-targeted antioxidant in an amount effective to provide said neuroprotective effect. The SkQ mitochondria-targeted antioxidant may be administered either prophylactically or for treatment with respect to brain pathologies other than brain trauma or stroke, and may be administered for treatment of brain trauma or stroke.

METHOD FOR MODERATELY INCREASING THE PROTON CONDUCTIVITY OF BIOLOGICAL MEMBRANES WITH THE AID OF MITOCHONDRIA-TARGETED DELOCALIZED CATIONS
US2011245207

The invention relates to biology and medicine, in particular, can be used in medicine for preparation of a pharmaceutical composition for specific, self-regulating uncoupling of mitochondria. The invention may be useful in treatment of diseases and conditions associated with violation of cellular metabolism, in treatment of obesity including its pathological forms, as well as in treatment of diseases associated with increased formation of free radicals and reactive oxygen species. In addition, the invention may be used in biotechnology for stimulation of growth of yeast and microorganisms as well as for stimulation of development of tissues and organs of plant and animal origin.

METHOD OF ACTING UPON ORGANISM BY TARGETED DELIVERY OF BIOLOGICALY ACTIVE SUBSTANCES INTO MITOCHONDRIA
WO2007046729 // US2008176929

This invention relates to biology and medicine and, in particular, can be used in medicine to make a pharmaceutical composition for targeted delivery of biologically active substances into mitochondria, driven by proton electro-chemical potential in the mitochondria. This invention also relates to the method to affect an organism by the targeted delivery of biologically active compounds to mitochondria. The invention can be useful in treatment of diseases or disorders associated with not normal functioning of mitochondria, in particular diseases associated with increased production of free radicals and reactive oxygen species.

COMPOSITION FOR REGENERATING AND STIMULATING GROWTH OF PLANTS AND FOR ADAPTING PLANTS TO DIFFERENT STRESS FACTORS
US8557733

The present invention relates to biotechnology. The invention can be used for stimulation of regeneration of plants from tissues and undifferentiated cells cultivated under artificial conditions. The present invention can also be applied in agriculture for acceleration of germination of seeds, increase in germination of aged, long-stored seeds as well as for increase of resistance of plants to biotic and abiotic stresses.

PHARMACEUTICAL AND COSMETIC COMPOSITIONS FOR ACCELERATED HEALING OF WOUNDS AND OTHER SURFACE DAMAGES
US2010292625

The invention relates to biology and medicine, in particular, it can be used in medicine for preparing a pharmacological composition used for accelerated healing of wounds and the damages by means of addressed (directed) delivery of biologically active agents to mitochondria by means electrochemical potential of hydrogen ions contained therein. Said invention can be also used for producing a composition useful in transplantation surgery for preserving transplantation material and for inhibiting rejection. Moreover, the invention can be used for producing a cosmetic agent for improving state of the skin and for the revitalisation and regeneration thereof.

PHARMACEUTICAL COMPOSITIONS USEFUL FOR PREVENTING AND TREATING ONCOLOGICAL DISEASES
US2010144680
