Chapter

Anti-Senescence Therapy

Raghad Alshadidi

Abstract

The development of therapeutic strategies aimed at the aging process of cells has attracted increasing attention in recent decades due to the involvement of this process in the development of many chronic and age-related diseases. Interestingly, preclinical studies have shown the success of a number of anti-aging approaches in the treatment of a range of chronic diseases. These approaches are directed against aging processes such as oxidative stress, telomerase shortening, inflammation, and deficient autophagy. Many strategies has been shown to be effective in delaying aging, including antiaging strategies based on establishing healthy lifestyle habits and pharmacological interventions aimed at disrupting senescent cells and senescent-associated secretory phenotype. Caloric restriction and intermittent fasting were reported to activate autophagy and reduce inflammation. In turn, immune-based strategies, senolytic agents, and senomorphics mediate their effects either by eliminating senescent cells through inducing apoptosis or by disrupting pathways by which senescent cells mediate their detrimental effects. In addition, given the association of the decline in the regenerative potential of stem cells with aging, many experimental and clinical studies indicate the effectiveness of stem cell transplantation in preventing or slowing the progress of age-related diseases by enhancing the repairing mechanisms and the secretion of many growth factors and cytokines.

Keywords: age-related disease, senescent-associated secretory phenotype, caloric restriction, senolytic agents, senomorphics, immune-based anti-senescence therapies

1. Introduction

Evidence of the involvement of cellular aging in the development of many age-related diseases, combined with the longevity benefits obtained from preventing the accumulation of senescent cells, raises the possibility that therapeutic targeting of senescent cells extends life span, improves overall health, and delays or prevents the development of age-related diseases. The investigation of the molecular mechanisms accounting for the development of senescent-associated secretory phenotype (SASP) and the ones providing senescent cells maintenance supplied insights for the development of mechanisms to target senescent cells. So far, many approaches have been proposed to target cell senescence, either by inducing the death of senescent cells or by blocking the SASP (**Figure 1**). This chapter provides an overview of senescent cells as an opportunity to intervene in the aging process and presents the various therapeutic anti-senescence paradigms in terms of their molecular mechanisms of action, efficacy, and safety.

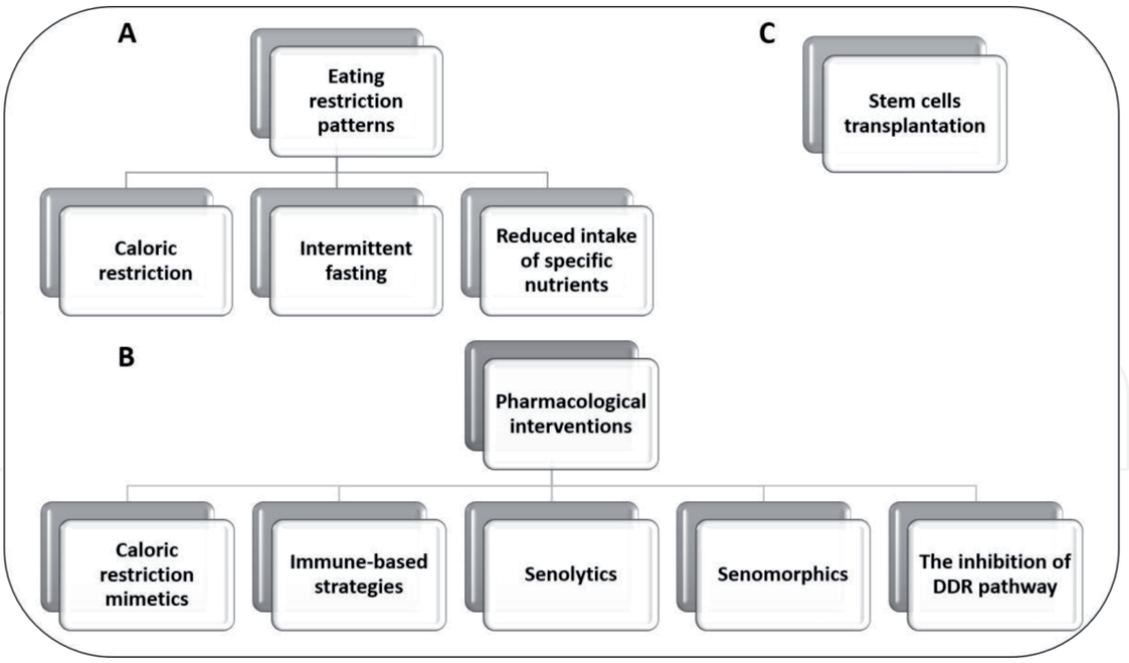

Figure 1.
Strategies targeting cellular senescence. (A) A number of dietary regimens, including caloric restriction, intermittent fasting, and reduced intake of certain nutrients, exert antiaging effects. (B) Pharmacological interventions have been developed to target senescent cells and limit their deleterious effects; certain natural or pharmacological compounds have been reported to exert the beneficial effects of CR, senolytic agents selectively induce apoptosis in senescent cells and block the prosurvival pathway, senomorphic agents interact with the components of the SASP, affecting their upstream pathway or their effectors, immune-based strategies aim to enhance the body's natural defense mechanisms or develop strategies to direct immune cells specifically toward senescent cells and/or overcome the mechanisms that senescent cells use to escape the immune system, and strategies targeting the DDR pathway aim to reduce the induction of cellular senescence. (C) Stem cell transplantation is thought to compensate for the decline in stem cell function, which is partly due to the senescence of stem cells. DDR, DNA damage response. (DDR is the abbreviation of DNA damage response).

2. Eating restriction patterns

A number of dietary regimens have been reported to prolong health span and longevity, in part by reducing their effects on senescence. These regimens include caloric restriction, intermittent fasting, and reduced intake of certain nutrients.

2.1 Caloric restriction (CR)

The underlying premise of caloric restriction (CR) is to reduce calorie availability by ~20–50%, while not consuming fewer vitamins, minerals, and other components of a healthy diet. It is well established that CR is a powerful intervention to extend the average and/or maximum life span of various species including yeast, flies, worms, fish, rodents, and rhesus monkeys [1], improve general health, and decrease aging-associated diseases [1]. Furthermore, data from natural and controlled investigations suggested the beneficial effects of CR on human longevity.

2.1.1 Mechanisms underlying CR antiaging effect

CR induces adaptations in the immune, neuroendocrine, and metabolic system by affecting a number of intracellular pathways; although human and animal observations and studies suggest that CR expands the life span, the mechanism underlying CR responses has not yet been established, and the followings explain some of the mechanisms, which mediate CR antiaging effects.

CR was reported to decrease cell senescence [2]. Given the fact that cell damage is the main inducer of senescence [3], the cytoprotective properties of CR may explain its senescence rate modulation effects. These effects include decrease in cellular stress [4], decrease in inflammation [5], and increased clearance of damaged proteins and organelles through the activation of autophagy [3]. In addition, CR decreases the mammalian target of rapamycin (mTOR) activity, which, in turn, plays a major role in the activation of cellular senescence [6]. Modulation of nutrient uptake pathways, including insulin-like growth factor (IGF), insulin, mTOR, and AMP-activated protein kinase (AMPK), mainly explains CR-mediated effects [6]. It was reported that CR decreases IGF signaling by inducing hypoglycemia and decreasing the level of insulin [6]. CR-mediated decrease in oxidative damage may be attributed to several mechanisms, including the increase in nitric oxide (NO) concentration [7], the increase in superoxide dismutase (SOD) activity [7], the decrease in reactive oxygen species (ROS) production [3], the decrease in protein glycation [3], the decrease in inflammatory proteins [3], and the increase in the expression of chaperone proteins [3]. Moreover, CR upregulates the expression of sirtuin-2 (sirt-2) [8], and NAD + -dependent protein deacetylases with antioxidant activity [9], the existence of extra copies of which was shown to extend the life span by up to 30%. CR exerts anti-inflammatory effect; a large number of investigations have shown that it reversed the effects of SASP and modulate age-related chronic inflammatory conditions [5]. This anti-inflammatory response can be attributed to the regulation of the activity of pro-inflammatory upstream signaling pathway molecules such as MAPKs (ERK, JNK, and p38), and NIK/IKKs and the suppression of key pro-inflammatory mediators such as NF-B, IL-1, IL-6, TNF, cyclooxygenase 2 (COX-2), and inducible nitric oxide synthase (iNOS) [5]. Intriguingly, CR was reported to induce a slight increase in circulating cortisol, which also account for the reduction in systemic inflammation [3]. Additionally, CR was reported to enhance DNA repair mechanism. This effect is mediated by the decrease of age-dependent decline in non-homologous end joining (NHEJ), the decrease of the age-dependent decline of polymerase alpha and beta and the increase of their fidelity, the induction of the base excision repair pathway (BER), and the enhancement of nucleotide excision repair (NER) [3]. Moreover, CR was shown to alter the phenotypes of stem cells, improve their function, and promote their self-renewal in mice [10]. Although most studies proposed the beneficial effects of CR, it is noteworthy to report the results of one study that suggest the negative impact CR has on brain integrity of mouse lemurs without affecting cognitive performances [11]. More investigations are required to evaluate the long-term effects of CR and create a comprehensive full image of the molecular and cellular mechanisms underlying its antiaging effect.

2.2 Other type of dietary restriction with antiaging effects

In addition to CR, other approaches have been proposed to reduce the effects of aging, including intermittent fasting and the reduced intake of certain nutrients. Intermittent fasting (IF) is an eating pattern that switches between fasting and eating on a regular schedule. It has been shown that IF has a protective effect against many age-related diseases such as obesity, hyperinsulinemia, hepatic steatosis, and inflammation [12]. Many types of IF have been proposed, including a fasting-mimicking diet, which has been reported to prolong the life span, reduce visceral fat, reduce cancer and skin damage, rejuvenate the immune system, and slow bone mineral loss in mice [13]. Other studies have shown that reduced intake of specific nutrients exerts antiaging effects. For example, reducing protein intake has been reported to reduce the risk of cancer death and overall mortality [12]. Interestingly,

it was suggested that the life span benefits of dietary restriction can be obtained from the reduced intake of certain amino acids such as tryptophan and methionine [14]. In addition, ketogenic diet, which primarily consists of high fats, moderate proteins, and very low carbohydrates, was widely reported to extend longevity and health span in mice [15].

3. Pharmacological interventions

The involvement of cell senescence in aging and the development of many age-related diseases has stimulated efforts to develop a number of strategies aimed at eliminating senescent cells and/or limiting their deleterious effects. These strategies include CR mimetics, senolytic agents, senomorphic agents, immune-based strategies, and strategies targeting the DNA damage response (DDR) pathway.

3.1 CR mimetics

CR mimetics are agents that have the beneficial effects of CR without the need to struggle with diet limitation; the followings are some of the most well-known CR mimetics.

3.1.1 Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is a natural plant-derived polyphenolic, phytoalexin compound found in grapes, cranberries, and peanuts. Resveratrol has been long used in traditional medicine, and now, it has wide range of applications in modern medicine thanks to their antioxidant, anti-inflammatory, anti-obesity, antidiabetic, antibacterial, anticarcinogenic, cardioprotective, and immunomodulating properties [16]. It is suggested that resveratrol exerts its antiaging effects through the activation of sirtuin-1 (sirt-1) [12]. One clinical study on healthy, obese men reported that 30 days of resveratrol supplementation elevated intramyocellular lipid levels, and decreased intrahepatic lipid content, circulating glucose, triglycerides, alanine-aminotransferase, inflammation markers, and systolic blood pressure with an improvement in HOMA index [17]. Another clinical study on overweight older individuals provides evidence that supplementation of resveratrol improves memory performance in association with improved glucose metabolism and increased hippocampal functional connectivity in older adults [3].

3.1.2 Metformin

Metformin is an FDA-approved antidiabetic agent used as a first-line drug for treating type 2 diabetes mellitus. The antiaging effects of metformin are well established in *Caenorhabditis elegans*, *Drosophila melanogaster*, and mice [5]. Metformin was reported to exert its antiaging effects through the activation of AMPK, which, in turns, leads to the inhibition of mTOR [18]. The wide application, well-known pharmacokinetics and acceptable toxicity encourage the use of metformin as an anti-aging drug [18]. However, further investigations are required since the metformin's antiaging effect has not been identified in humans yet [5].

3.1.3 Rapamycin

Rapamycin is an FDA-approved immunosuppressant, which is extensively used following kidney and liver transplants and to treat certain types of cancers and

complications of tuberous sclerosis [19]. The antiaging effect of rapamycin is well established for several years in model organisms including mice [19] and is mediated through the direct inhibition of the kinase activity of mTOR [5]. Despite its widely reported antiaging effect, certain side effects pose a barrier to the use of rapamycin as antiaging agent; this includes hyperlipidemia, hypercholesterolemia, and hypertriglyceridemia, glucose intolerance, insulin resistance and new-onset diabetes, anemia and thrombocytopenia, dermatological events, gastrointestinal disorders, sinusitis, respiratory and urinary infections, and testicular dysfunction [19]. To minimize these side effects, a number of alternative treatment regimens have been developed, including intermittent rapamycin [19]. In addition, fewer side effects have been reported after the administration of rapamycin analogs with a reduced effect on glucose metabolism, such as everolimus and temsirolimus [19].

3.2 Enhancement of the immune clearance of senescent cells

The immune system has its own internal targeting mechanism for senescent cells. Multiple components of the immune system target senescent cells, including NK cells, T cells, and macrophages [20]. The immunogenicity of senescent cells, combined with the age-related decline in immune function, raises the potential for strategies such as boosting the immune system or targeting the inhibitory mechanisms by which senescent cells escape the immune system to be exploited to enhance the clearance of senescent cells [20]. In this context, many strategies have been proposed, including blocking the inhibitory decoy receptor 2 (DR2) and stimulating the innate immune response using the viral infection stimulator poly (I:C) [21]. In addition, the implementation of the advances in genetic engineering by designing chimeric antigen receptor T (CAR T) cells specific for senescent cells is a promising approach. However, the lack of overlap between the extracellular markers identified by different studies is an obstacle for designing CAR T cells specific for senescent cells [20].

3.3 Senolytic agents

Senolytic agents target specifically senescent cells, and they are considered promising agents for delaying aging processes as they target the fundamental mechanisms that are contributors for many diseases. Dasatinib, quercetin, and fisetin are the most well-studied senolytic agents [22]. Dasatinib is a second-generation tyrosine kinase inhibitor that is used for the treatment of CML and AML [23]. Quercetin is a polyphenolic flavonoid compound with antioxidant properties, which exerts preventive effects for various diseases, such as osteoporosis, some forms of cancer, tumors, and lung and cardiovascular diseases [24]. Fisetin is a flavonol that shows potential as an anti-inflammatory, chemopreventive, and chemotherapeutic agent [25]. Senolytic agents were discovered by scanning using bioinformatic approach to find drugs that disrupt the senescent cell anti-apoptotic pathways (SCAPs) network nodes, which differ from the one-target one-drug approach. Thereby, an important characteristic of these agents is their targeting to multiple SCAP network nodes rather than acting upon single or limited targets, which, in turn, reduces the off-target apoptotic effects on nonsenescent cell types [22]. *In vivo* studies showed that these agents reduce senescent cells by apoptosis; specifically, the underlying molecular mechanisms by which senolytic agents mediate their effects are lowering of p16Ink4a, targeting Bcl-2 family, hypoxia-inducible factor 1-alpha (HIF-1a), and other SCAPs network components [22]. Since dasatinib and quercetin are senolytics for different cell lines, it is suggested that the effects of senolytic drugs depend on

the type of senescent cells [22]. Interestingly, the combination of dasatinib + quercetin was reported to be senolytic for cell lines in which neither dasatinib nor quercetin are senolytics on their own [22]. Senolytic drugs were reported to improve cardiac function in mice, enhance insulin sensitivity, reduce the adipose tissue inflammation, and alleviate many age-related diseases in which the accumulation of senescent cells plays role in its pathogenesis including Alzheimer's disease, chronic lung diseases, osteoporosis, and intervertebral disk disease [22]. As senolytic drugs are new agents, special cautions are considered while testing them in clinical trials; therefore, they entered only clinical trials for serious diseases that lack effective treatment strategies [22]. The results of a clinical trial where dasatinib + quercetin were administered orally by patients with diabetes complicated by renal dysfunction showed decrease in senescent cells and adipose tissue inflammation [22]. Many clinical trials are now ongoing or planned including trials of dasatinib + quercetin for the treatment of many senescence and age-related diseases [22]. So far, senolytic agents are not used out of clinical trials as their effects are under investigation [22]. However, depending on the results of clinical trials, senolytic agents can have further applications in the future to delay and prevent the developing of senescence- and age-related diseases in those subjects, in whom the presence of senescent cells can be detected in body fluids or by imaging [22].

3.4 Senomorphic agents

Senomorphic agents are an alternative approach to senolytics, the concept behind this approach is to disrupt pathways by which senescent cells mediate its detrimental effects without eliminating the cells. For this purpose, neutralizing antibodies targeting SASP components or their receptors have been developed [26]. Approaches based on the transcriptional modulation of the expression of SASP factors were developed to reduce SASP production [27].

In addition, based on the fact that mTOR activation promotes SASP production through translation of subsets of mRNA that stabilizes many cytokine-encoding transcripts, certain mTOR inhibitors can be considered senomorphic agents [20]. For example, rapamycin, which exhibits CR-mimicking effects, was reported to decrease SASP production by inhibiting mTOR [20]. Besides, apigenin and kaempferol were shown to attenuate SASP production through their modulating effects on NF-κB signaling [20].

Senolytic agents have advantages over senomorphics, which include the possibility to take them intermittently and the reduction of the likelihood of senescence bypassing mutations that can promote tumorigenesis, since these agents eliminate senescent cells rather than targeting SASP production [20]. However, the still undetermined safety of prolonged or repeated administration of senolytic agents combined with an emerging study report on the likelihood of senolysis damage to cells with structural functions [28] makes senomorphics a considerable alternative to senolytic agents.

3.5 Targeting senescent cells by inhibiting the DNA damage response (DDR) pathway

DNA damage response (DDR) pathway is a signaling cascade that is activated in response to DNA damage. Given the evidence that activation of the DDR pathway triggers cell senescence, antisense oligonucleotides have been developed to inhibit telomeric DDR. Results from *in vitro* and *in vivo* studies in mice have provided evidence for the effectiveness of this approach [20].

4. Stem cell transplantation

Cell senescence has been implicated in the decline of stem cells' function and proliferation potential [20], which, in turn, contributes to aging and the development of age-related disease [29]. Therefore, stem cell transplantation has been proposed as a strategy to treat many age related disease including Alzheimer's disease [30], macular degeneration [31], osteoarthritis [32], and frailty [33]. The beneficial effects of this strategy are exerted through the compensation of aging-related decline in stem cell function, the regulation of inflammation and immune responses, as well as the secretion of therapeutic cytokines and factors [29]. The promising results of the preclinical experiments on mice models [33] lead to its translation to clinical trials. Phases I and II clinical trials were conducted to investigate the efficiency of mesenchymal stem cells (MSCs) infusion in alleviating frailty and the results showed safety profile and promising therapeutic efficacy [33]. A number of clinical trials provided evidence of the efficiency of MSCs therapies for the treatment of osteoarthritis [32]. Furthermore, a phase I clinical study supports the efficiency and safety of the transplantation of embryonic stem cell-derived retinal pigment epithelium patches as a regenerative strategy for age-related macular degeneration [31]. Although the results of preclinical and clinical studies provide initial evidence of the efficiency of stem cell transplantation for the treatment of age-related diseases, the concerns of stem cells tumorigenicity impose the need for further research and clinical trials with the consideration of the framework regulatory agencies to ensure the safety of participants [29].

5. Conclusion

Despite initial evidence for the safety and efficacy of a number of antiaging therapeutic approaches to combat the aging process, the novelty of this area of study stresses the need to conduct further preclinical and clinical study to understand the efficacy, safety, and long-term effects of anti-senescence therapeutic strategies in addition to the optimization of the most effective strategy with minimal off-targets and side effects. Further research in terms of the molecular mechanism of senescence and anti-senescence therapeutic strategies could reshape our view of health management during aging, offering many therapeutic options in the context of increasing longevity and preventing or alleviating many age-related diseases.

Acronyms and abbreviations

AMPK	AMP-activated protein kinase
CAR-T	cell chimeric antigen receptor (CAR) T cell
COX-2	cyclooxygenase 2
CR	caloric restriction
DDR	DNA damage response
DR2	decoy receptor 2
HOMA index	homeostatic model assessment index
IF	intermittent fasting
IGF 1	insulin-like growth factor 1
IKK	inhibitor of NF-kappaB kinase
iNOS	inducible nitric oxide synthase
MAPK	mitogen-activated protein kinase

mTOR	the mammalian target of rapamycin
NIK	NF-κB-inducing kinase
NO	nitric oxide
SASP	senescent-associated secretory phenotype
SCAP	senescent cell anti-apoptotic pathways
sirt-2	sirtuin
SOD	super oxide dismutase

Author details

Raghad Alshadidi
Kazan Federal University, Kazan, Russia

*Address all correspondence to: rag.rsh997@gmail.com

References

[1] Fontana L, Partridge L, Longo VD. Dietary restriction, growth factors and aging: From yeast to humans. Science. 2010;**328**(5976):321. DOI: 10.1126/SCIENCE.1172539

[2] Fontana L, Nehme J, Demaria M. Caloric restriction and cellular senescence. Mechanisms of Ageing and Development. 2018;**176**:19-23. DOI: 10.1016/j.mad.2018.10.005

[3] Witte AV, Kerti L, Margulies D, Flöel A. Effects of resveratrol on memory performance, hippocampal functional connectivity, and glucose metabolism in healthy older adults. The Journal of Neuroscience. 2014;**34**(23): 7862-7870. DOI: 10.1523/JNEUROSCI.0385-14.2014

[4] Barja G. Aging in vertebrates, and the effect of caloric restriction: A mitochondrial free radical production-DNA damage mechanism? Biological Reviews of the Cambridge Philosophical Society. 2004;**79**(2):235-251. DOI: 10.1017/S1464793103006213

[5] Kim DH, Bang E, Jung HJ, Noh SG, Yu BP, Choi YJ, et al. Anti-aging effects of calorie restriction (CR) and CR mimetics based on the senoinflammation concept. Nutrients. 2020;**12**(2):422. DOI: 10.3390/nu12020422

[6] Weichhart T. mTOR as regulator of lifespan, aging and cellular senescence. Gerontology. 2018;**64**(2):127. DOI: 10.1159/000484629

[7] Stankovic M, Mladenovic D, Ninkovic M, Vucevic D, Tomasevic T, Radosavljevic T. Effects of caloric restriction on oxidative stress parameters. General Physiology and Biophysics. 2013;**32**:277-283. DOI: 10.4149/gpb_2013027

[8] Xiang L, He G. Caloric restriction and antiaging effects. Annals of Nutrition & Metabolism. 2011;**58**(1):42-48. DOI: 10.1159/000323748

[9] Singh CK, Chhabra G, Ndiaye MA, Garcia-Peterson LM, Mack NJ, Ahmad N. The role of sirtuins in antioxidant and redox signaling. Antioxidants & Redox Signaling. 2018;**28**(8):643-661. DOI: 10.1089/ARS.2017.7290

[10] Schultz MB, Sinclair DA. When stem cells grow old: Phenotypes and mechanisms of stem cell aging. Development. 2016;**143**(1):3. DOI: 10.1242/DEV.130633

[11] Pifferi F, Terrien J, Marchal J, Dal-Pan A, Djelti F, Hardy I, et al. Caloric restriction increases lifespan but affects brain integrity in grey mouse lemur primates. Communications Biology. 2018;**1**:30. DOI: 10.1038/s42003-018-0024-8

[12] Hanjani NA, Vafa M. Protein restriction, epigenetic diet, intermittent fasting as new approaches for preventing age-associated diseases. International Journal of Preventive Medicine. 2018;**9**:58. DOI: 10.4103/IJPVM.IJPVM_397_16

[13] Brandhorst S et al. A periodic diet that mimics fasting promotes multi-system regeneration, enhanced cognitive performance, and healthspan. Cell Metabolism. 2015;**22**(1):86-99. DOI: 10.1016/J.CMET.2015.05.012

[14] Grandison RC, Piper MDW, Partridge L. Amino-acid imbalance explains extension of lifespan by dietary restriction in *Drosophila*. Nature. 2009;**462**(7276):1061-1064. DOI: 10.1038/nature08619

[15] Roberts M, Wallace M, Tomilov A, Zhou Z, Marcotte G, Tran D, et al. A ketogenic diet extends longevity and healthspan in adult mice. Cell

Metabolism. 2017;**26**(3):539-546.e5. DOI: 10.1016/J.CMET.2017.08.005

[16] Gianchecchi E, Fierabracci A. Insights on the effects of resveratrol and some of its derivatives in cancer and autoimmunity: A molecule with a dual activity. Antioxidants. 2020;**9**(2):91. DOI: 10.3390/ANTIOX9020091

[17] Timmers S, Konings E, Bilet L, Houtkooper R, Weijer T, Goossens G, et al. Calorie restriction-like effects of 30 days of Resveratrol (resVida™) supplementation on energy metabolism and metabolic profile in obese humans. Cell Metabolism. 2011;**14**(5):612-622. DOI: 10.1016/J.CMET.2011.10.002

[18] Onken B, Driscoll M. Metformin induces a dietary restriction-like state and the oxidative stress response to extend *C. elegans* healthspan via AMPK, LKB1, and SKN-1. PLoS One. 2010;**5**(1): e8758. DOI: 10.1371/JOURNAL.PONE.0008758

[19] Apelo S, Lamming D. Rapamycin: An inhibitor of aging emerges from the soil of Easter Island. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2016;**71**(7):841-849. DOI: 10.1093/GERONA/GLW090

[20] Di Micco R, Krizhanovsky V, Baker D. Cellular senescence in ageing: From mechanisms to therapeutic opportunities. Nature Reviews. Molecular Cell Biology. 2021;**22**(2):75-95. DOI: 10.1038/s41580-020-00314-w

[21] Ovadya Y, Krizhanovsky V. Strategies targeting cellular senescence. The Journal of Clinical Investigation. 2018;**128**(4):1247-1254. DOI: 10.1172/JCI95149

[22] Gerdes EOW, Zhu Y, Tchkonia T, Kirkland JL. Discovery, development, and future application of senolytics: Theories and predictions. The FEBS Journal. 2020;**287**(12):2418. DOI: 10.1111/FEBS.15264

[23] Hořínková J, Šíma M, Slanař O. Pharmacokinetics of Dasatinib. Prague Medical Report. 2019;**120**(2-3):52-63. DOI: 10.14712/23362936.2019.10

[24] Xu D, Hu M-J, Wang Y-Q, Cui Y-L. Antioxidant activities of Quercetin and its complexes for medicinal application. Molecules. 2019;**24**(6):1123. DOI: 10.3390/MOLECULES24061123

[25] Grynkiewicz G, Demchuk OM. New perspectives for fisetin. Frontiers in Chemistry. 2019;**7**:697. DOI: 10.3389/FCHEM.2019.00697

[26] Liu S, Uppal H, Demaria M, Desprez P-Y, Campisi J, Kapahi P. Simvastatin suppresses breast cancer cell proliferation induced by senescent cells. Scientific Reports. 2015;**5**(1):1-11. DOI: 10.1038/srep17895

[27] Cuollo L, Antonangeli F, Santoni A, Soriani A. The senescence-associated secretory phenotype (SASP) in the challenging future of cancer therapy and age-related diseases. Biology. 2020;**9**(12):1-16. DOI: 10.3390/BIOLOGY9120485

[28] Grosse L, Wagner N, Emelyanov A, Molina C, Lacas-Gervais S, Wagner K, et al. Defined p16 high senescent cell types are indispensable for mouse healthspan. Cell Metabolism. 2020;**32**(1):87-99.e6. DOI: 10.1016/J.CMET.2020.05.002

[29] Nguyen H, Zarriello S, Coats A, Nelson C, Kingsbury C, Gorsky A, et al. Stem cell therapy for neurological disorders: A focus on aging. Neurobiology of Disease. 2019;**126**:85. DOI: 10.1016/J.NBD.2018.09.011

[30] Vasic V, Barth K, Schmidt MHH. Neurodegeneration and neuro-regeneration Alzheimer's disease and stem cell therapy. International Journal

of Molecular Sciences. 2019;**20**(17):4272. DOI: 10.3390/IJMS20174272

[31] da Cruz L et al. Phase 1 clinical study of an embryonic stem cell-derived retinal pigment epithelium patch in age-related macular degeneration. Nature Biotechnology. 2018;**36**(4):328-337. DOI: 10.1038/NBT.4114

[32] Freitag J, Bates D, Boyd R, Shah K, Barnard A, Huguenin L, et al. Mesenchymal stem cell therapy in the treatment of osteoarthritis: Reparative pathways, safety and efficacy—A review. BMC Musculoskeletal Disorders. 2016;**17**(1):230.DOI:10.1186/S12891-016-1085-9

[33] Schulman I, Balkan W, Hare J. Mesenchymal stem cell therapy for aging frailty. Frontiers in Nutrition. 2018;**5**:108. DOI: 10.3389/FNUT.2018.00108