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Senolytics and their effects on various diseases

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ABSTRACT

Senescence is the result of a process that is physiological for cells. With aging, there is an increase in the number of senescent cells in organisms, and these cells produce a number of compounds known as senescence-associated secretory phenotype (SASP). These compounds secreted by senescent cells cause healthy cells in the microenvironment to exposure senescence. Therefore, preventing the accumulation of senescent cells in tissues is important for healthy cells. Senolytics are compounds that can specifically eliminate senescent cells. One of the most important differences between a cell in its normal physiological process and a senescent cell is that senescent cells are resistant to apoptosis. Although senolytics have different mechanisms of action, they jointly target the anti-apoptotic pathways of the cells and the compounds in these pathways, thereby enabling the senescent cells to undergo apoptosis and be destroyed. In addition, accumulation of senescent cells in tissues increases the risk of susceptibility to various chronic diseases, especially cardiovascular diseases, neurodegenerative diseases, cancer and kidney diseases. Therefore, it is forecasted that inhibiting the accumulation of senescent cells in tissues may reduce the risk of disease. In this review study, the effects of senolytic compound examples such as Dasatinib, Quercetin, Navitoxlac (ABT-263) and Fisetin on cardiovascular diseases, neurodegenerative diseases, cancer, kidney diseases and inflammation were briefly summarized.

Keywords: Chronic Diseases, SASP, Senescence, Senolytic

1. INTRODUCTION

Aging is an inevitable end for living things and one of the biggest risk factors for many diseases. Aging is actually expressed in two terms: aging and senescence. While aging refers to aging at the organism level, senescence describes cellular aging. In this context, it can be concluded that aging occurs in organisms with the increase of senescence. Also there are important differences between aging and senescence. Aging is a process, it happens over time. Senescence is a process that starts from embryogenesis and is a necessary mechanism for important and fundamental events in development and wound healing (Zia et al., 2021). The concept of senescence was first used by Leanord Hayflick. Leonard Hayflick and Paul Moorhead have observed through their study in human fibroblast cells that cells do not divide forever in culture, their ability to divide continues up to a certain limit. This observation has been given to the literature as the 'Hayflick Limit'. Cells have a certain capacity to divide following their physiological processes and this is known as the 'Hayflick Limit'. After an average of 40-60 divisions, cells reach the Hayflick limit and cells in their normal

physiological process enter senescence (Hayflick, 1965).

Senescence, which is the result of physiological processes of cells, can be induced by various mechanisms and factors. Examples of these are exposure to ionizing radiation, chemotherapy agents (e.g etoposide, doxorubicin), reactive metabolites (e.g ROS, NOS), inflammatory cytokines (e.g IL-6, IL-1), injury and pathogen-associated molecules (e.g HMGB1, LPS, viral RNA), oncogene activation and telomere erosion (Zhang et al., 2021). In addition, replicative stress, genotoxic stress, oxidative stress, oncogene activation and inflammatory factors can also be effective in the senescence of cells (Y. Wang et al., 2021; Zhang et al., 2021). Cells that have undergone senescence are called senescent cells (Childs et al., 2017). These cells differ from non senescent cells. Senescent cells enter a state of cell cycle arrest characterized by distinct biomarkers such as enlarged morphology, increased β-galactosidase activity, release of a number of inflammatory SASPs, formation of epigenetic and DNA damage-related changes. These features and markers are shown in detail in Table 1.

The most basic feature that should not be forgotten for senescent cells is that although these cells show growth inhibition, they are still metabolically active. This metabolic activity confers on cells their unique senescence-associated secretory phenotype (SASP) (Birch and Gil, 2020). Senescent cells may adversely affect the tissue microenvironment and adjacent healthy cells, mainly by secreting proinflammatory

Table 1: Characteristic features and markers of senescent cells

Characteristic Features	Marker	Explanation
Proliferative arrest	Low expression of Ki-67	Ki-67 is a proliferation marker, this marker is seen as a reliable marker especially in cancer studies with the change in expression levels at certain stages of the cell cycle (Sun and Kaufman, 2018).
Secretion of senescence-associated secretory phenotype (SASP)	Various cytokine, chemokine and protease enzymes	SASP components secreted by senescent cells can cause inflammation, inhibition of stem cells and the mechanism of apoptosis (Ohtani, 2022; Wyld et al., 2020)
Altered metabolism, including increased β-galactosidase activity, which is part of carbohydrate metabolism	Measuring ß-galactosidase levels (SA-ßgal) (de Mera-Rodríguez et al., 2021a)	B-gal is an enzyme involved in the metabolism of galactose-containing carbohydrates. İt has been determined that the activity of this enzyme increases with aging. Among the aging markers, ß gal is considered one of the best characterized markers (de Mera-Rodríguez et al., 2021b; Debacq-Chainiaux et al., 2009).
Changes in cell morphology	Observation of cells under a light microscope	Senescent cells are morphologically larger than non senescent cells (Beck et al., 2020).
Persistent activation in DNA damage response	Activation of tumor supressors such as p53, $p16^{INK4a}$, cyclins and cyclin-dependent kinases	Along with senescence, changes occur in the expression of cyclin and cyclin-dependent kinases, which are primarily regulators of the cell cycle, as well as p53 and $p16^{INK4a}$, which are tumor supressor genes (Gire and Dulic, 2015; Mijit et al., 2020; Rayess et al., 2012).

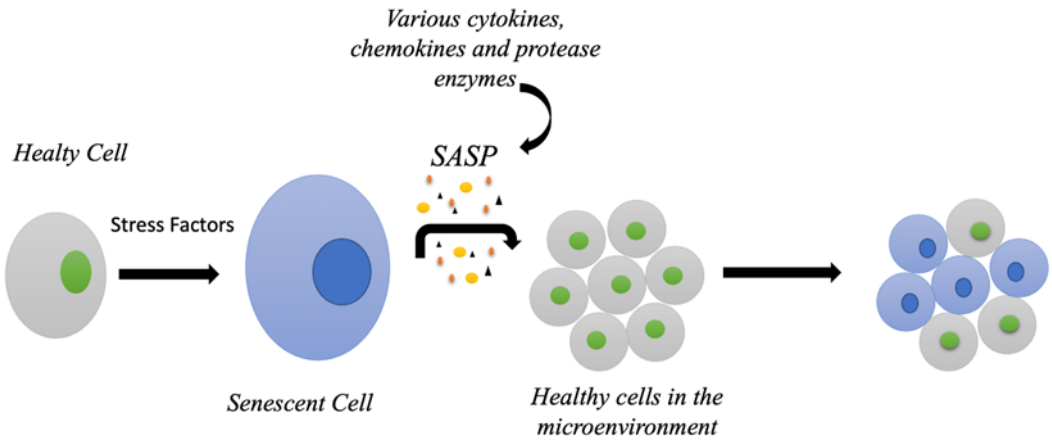

Figure 1: Various factors secreted by the senescent cell under the influence of stress factors and its effect on the healthy microenvironment (Lee et al., 2021)

cytokines, triggering tissue dysfunction or adverse consequences. This effect is shown in Figure 1. This effect of senescent cells increases the risk of various chronic diseases such as cardiovascular diseases, neurodegenerative diseases and kidney diseases.

The World Health Organization (WHO) reported that the elderly population is gradually increasing and this increase is occurring faster than expected. With the increase in the elderly population, the spread of chronic diseases also increases. WHO reports that more than 90% of individuals over the age of 65 have at least one chronic disease, such as cardiovascular disease, cancer, dementia, diabetes, osteoarthritis, and osteoporosis, while more than 70% have at least two such conditions. The occurrence of susceptibility to diseases with aging both reduces the quality of life of individuals and causes an economic burden for countries. For this reason, it is necessary to improve the risk of developing diseases due to the accumulation of senescent cells. Senolytics are a group of therapeutic compounds that specifically select senescent cells and eliminate them (Kirkland and Tchkonia, 2020). These substances are able to do this effect by taking advantage of a very important property of senescent cells. This feature is that senescent cells are resistant to apoptosis (Cerella et al., 2016). Senescent cells that are resistant to apoptosis act by activating the mechanisms in anti-apoptotic pathways and molecules in this pathway or by suppressing the activation of molecules in the apoptotic pathway. In addition, considering the diversity of senescent cells, there are more effective senolytics on the cell type and different cell lines where each senolytic drug is more effective.

The first drug whose senolytic effect was discovered was Dasatinib (D). Dasatinib is particularly effective on aging preadipocytes. Before the discovery of its senolytic effect, dasatinib was used clinically in the treatment of advanced chronic leukemia, acute lymphoblastic leukemia, and chronic myeloid leukemia (Zhang et al., 2021). Quercetin (Q) BCL-2, another identified senolytic, is a naturally occurring flavonoid compound that targets the PI3K/AKT pathway, insulin/IGF-1, HIF-1α pathways. It has been shown to be more effective on senescent endothelial cells (Hwang et al., 2018). As can be seen in the examples of Dasatinib and Quercetin, the cell type, target pathway and molecules that each senolytic drug acts on differ.

In addition to quercetin, one of the natural senolytics is gingerenone. Gingerenone, a very new senolytic, is ginger extract. Among the basic components of ginger, gingerenone and 6-shogaol show senolytic effect. As in studies D and Q, gingerenone and 6-shogaol showed more effective senolytic effect in combination. This result obtained in the study with WI -38 human fibroblasts showed that senolytics induce apoptosis and gingerenone A has a significant effect in suppressing SASP. In addition, it has been reported that gingerenone A shows senolytic effect by reducing the expression of the anti-apoptotic protein Bcl-xl. In addition to the Bcl-xL suppression effect, it

is also important that gingerenone A increases p53 gene expression (Moaddel et al., 2022; Rad & Grillari, 2024).

Another natural senolytic, fisetin, like quercetin, is a flavonoid compound from the family of natural pigments known as polyphenols. Fisetin, which is found in various fruits and vegetables, especially strawberries, enables senescent cells to go to apoptosis with the change in iron and copper ions concentration in the cell. More Fe and Cu ion accumulation occurs in senescent cells compared to normal cells. The reason for this is that structures such as Atp7a, which are responsible for the uptake of copper and iron into the cell, become dysfunctional with aging. With the application of fisetin and quercetin, which are senolytic agents in senesent cells, copper and iron accumulated in the cell are subjected to reduction-oxidation (redox) reactions with fenton and fenton-like reactions, and many reactive oxygen species are formed as a result of these reactions. Reactive oxygen species formed by fisetin and quercetin are H2O2 and OH-. In particular, excessive accumulation of hydroxyl (OH-) radical in the cell causes this radical to attack macromolecules, mainly DNA, and thus the cell goes into apoptosis. Since the accumulation of copper and iron ions in the normal cell is at a level that can be tolerated by the mechanisms developed by the cell itself, the normal cell can continue its physiological process (Y. Wang et al., 2021). Finally, considering the different targets of senolytics, it is noteworthy whether the use of these substances in various chronic diseases will affect the course of the disease and improve the quality of life of the individual. In this review study, the effects of senolytics, which are new generation drugs, on various chronic diseases are discussed.

2. SENOLYTICS AND THEIR EFFECTS ON VARIOUS DISEASE

2.1. Senolytics and cardiovascular diseases

Cardiovascular diseases (CVD) are diseases that threaten heart health and affect the circulatory system (Özkan et al., 2019).The risk of CVD increases with aging, and CVD is reported as the cause of death in 40% of individuals over the age of 65 (Owens et al., 2021; Virani et al., 2021). Examples of this group of diseases are coronary heart disease, cerebrovascular disease, rheumatic heart disease, heart failure, hypertension, congenital heart disease, deep vein thrombosis, and pulmonary embolism (Özkan et al., 2019). Adverse conditions such as heart failure and valvular heart disease, an increase in the prevalence of atherosclerosis, coronary artery stenosis and subsequent myocardial infarction and thoracic aortic aneurysm are seen with aging. In addition, as a result of increasing mitochondrial damage with aging, hypertrophy and fibrosis occur (Iske et al., n.d.). As the population continues to age, the incidence of CVD is expected to increase rapidly, and it is thought that this situation will create a serious burden both in terms of health and economy in the global sense.

Senolytics as a new approach in CVD is a treatment tool that is still considered new, but at the same time it is seen as promising. Zhu et al. targeted siRNA-mediated inhibition of components of senescent cells and used dasatinib and quercetin in their study. It has been determined that the combined application of dasatinib and quercetin is more effective in vivo compared to their individual use. D and Q administration has been shown to reduce lung fibrosis and hepatic stenosis, improve vasomotor function, ventricular function, and neurogenesis, and prevent age-related bone loss, anxiety-related behavior, and increase life expectancy in preclinical models (Zhu et al., 2015).

2.2. Neurodegenerative diseases

Some neurological diseases, especially Alzheimer's and Parkinson's diseases incidence increase with aging. Senolytic substance fisetin clears ROS products; it has also been reported to protect primary neurons of rats against glutamate toxicity, hypoglycemia, and oxidative damage by improving glutathione (GSH) metabolism (Ishige et al., 2001; Pal et al., 2016). It has also been reported that fisetin administration reduces aluminum-induced neurotoxicity and increases GSH levels in brain

tissues (especially cortex and hippocampus) of mice by increasing the production of endogenous antioxidants such as superoxide dismutase, catalase, and glutathione s-transferase (Pal et al., 2016). In a different study, a significant improvement in learning and memory was also observed in mice fed a fisetin-containing diet (500 mg/kg food) for 10 months compared to mice fed a fisetin-free diet. Fisetin is a natural flavonoid compound found in fruits and vegetables (mostly 160 ug/g in strawberries) and is a senolytic substance (Y. Wang et al., 2021). In a study in rats, a diet containing strawberry extract was found that rats could retain spatial information (hippocampal-mediated behavior) better than the control group. Furthermore, fisetin has been shown to have the potential to protect as well as increase cell survival, induce differentiation and enhance long-term memory in nerve cells (Maher, 2009; Pal et al., 2016).

2.3. Senolytics and cancer

Cancer is the second disease with the highest mortality rate in the world (Demirbaş Karadeniz et al., 2021). The most common types of cancer are lung, breast and colorectal cancers. Lung, liver and stomach cancers are the leading cancer-related deaths (Ferlay et al., 2015). To combat this disease, mainly chemotherapy, stem cell therapy, radiotherapy, complementary treatment methods (for example, aromatherapy) and surgical methods are used. These treatment methods can be applied alone or in combination, depending on the patient's current condition and the prognosis of the disease. The use of senolytics for cancer treatment has been tried relatively recently. As mentioned in Table 1, one of the distinguishing features of senescent cells is the occurrence of changes in gene expression. Changes in gene expression cause changes in chromatin structure and as a result, disorders in the apoptosis mechanisms of cells (Sieben et al., 2018). Senescent cells usually have increased levels of anti-apoptotic BCL2 family proteins. Compounds targeting this family of proteins have been extensively investigated in senolytic therapy. Various studies have shown that the senolytics navitoclax (ABT263) and ABT737, inhibitors of BCL-2, BCL-XL and BCL-W, reactivate the apoptotic pathway and eliminate many types of senescent cells, including senescent cancer cells. (L. Wang et al., n.d.). Fisetin has been shown to induce apoptosis in lung cancer via mitochondrial pathways. Furthermore, fisetin induce DNA fragmentation, ROS generation and apoptosis in NCI-H460 (lung cancer cell line) cells through a decrease in Bcl-2 and an increase in Bax expression (Lall et al., 2016).

2.4. Senolytics and kidney diseases

With aging, as with other organs, there are a number of changes and dysfunction in the kidney (Epstein, 1996). Senolytic drugs such as dasatinib and quercetin have been reported to improve diabetes-related insulin resistance and other chronic kidney diseases in mice by disabling the anti-apoptotic cell survival pathways of aging cells. In the first clinical study on the application of senolytics, D+Q alleviated the physical dysfunction in idiopathic pulmonary fibrosis (IPF), a disease associated with cellular aging and with a fatal effect (Hickson et al., 2019).

2.5. Senolytics and inflammation

Inflammation is a response of the immune system to harmful (radiation, various pathogens, toxic compounds, damaged cells) components and stimuli in the body (Chen et al., 2018). With aging, there is an increase in the number of senescent cells in the organism. With this increase, the senescence-associated secretory phenotype (SASP) secreted by senescent cells causes tissue infiltration of immune cells, causing chronic low-grade inflammation, which in turn causes age-related diseases. In a study in male C57BL/6 mice, dasatinib and quercetin were administered and it was shown that D and Q reduced adipose tissue inflammation and improved systemic metabolic function in aged mice (Islam et al., 2023). In another study using two different zebrafish models, the roles of the senolytic drugs dasatinib, navitoclax and venetoclax in inflammation were investigated. Study findings show that applied senolytics have an anti-inflammatory effect by providing healing of chronic inflammation (Hernández-Silva et al., 2022).

3. RESULT AND DISCUSSION

Senolytics are therapeutic approaches that target accumulated senescent cells during the aging process, aiming to eliminate these cells. Senescent cells are cells associated with aging and various pathological conditions, contributing to inflammation and tissue deterioration. The potential benefits of senolytics include improving the quality of life in elderly individuals, enhancing or delaying the progression of chronic diseases, reducing inflammation, and overall health preservation. Such therapies can offer potential treatment options for various health issues such as cardiovascular diseases, neurodegenerative diseases, cancer, kidney diseases, and inflammation. As emphasized in our review, it is of significant importance to conduct more in vivo and in vitro studies on the effects of senolytics. Different senolytic agents' effects on various disease groups, their mechanisms, and potential side effects should be explored in more detail. The results of such studies, when incorporated into the literature, can enhance the knowledge and understanding within the scientific community in this field. Additionally, for senolytic therapies to transition into clinical usage, more research, development, and clinical trials are necessary. The safety, efficacy, and long-term outcomes of these therapies can be better understood through larger-scale clinical studies. In conclusion, it can be stated that senolytics present a potential approach in treating age-related diseases, and our review aims to contribute to the literature by highlighting the significance of this area.

4. CONCLUSION

In this review, the effects of senolytic substances on cardiovascular diseases, neurodegenerative diseases, cancer, kidney diseases and chronic inflammation by targeting senescent cells that increase and accumulate in tissues due to aging were evaluated. The findings suggest that senolytics can alleviate the symptoms and effects of age-related diseases, reduce the risk of developing these diseases, and improve quality of life. However, many more studies are needed in this field. Both in vitroand in vivo studies should be increased and added to the literature. Studies have shown that the combined use of D and Q senolytics provide more effective results than using these senolytics alone. This creates a new question mark in minds and arouses curiosity about the combined applications of different senolytic substances. With the increase in the research to be done, both the identification of new senolytic substances should be ensured and the results of the combined use of different senolytic substances, as in the case of D and Q, should be investigated. Another question in this field of research is the mechanism of action of senolytic substances. Senolytic compounds have various mechanisms of action such as induction of apoptosis, which is programmed cell death, suppression of anti-apoptotic compounds and pathways, provision of ROS accumulation and mitochondrial dysfunction, enhancement of intracellular stress responses and proteolysis. However, these mechanisms have not been specifically elucidated for each senolytic substance. These mechanisms need to be elucidated with new studies. In this way, specific pathways and molecules can be targeted and new strategies can be developed in the treatment of diseases.

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