Review Article

Biotechnological Application of Natural Products for the Control of Cell Senescence and Skin Cancer

Gabriel Athayde Ramirez[a], Tania Araujo Viel[a, b, *]

[a] Undergraduation Course on Biotechnology, School of Arts, Sciences and Humanities, University of Sao Paulo

[b] Laboratory of Neuropharmacology of Aging, School of Arts, Sciences and Humanities, University of Sao Paulo

Correspondence to: Dr. Tania Viel, School of Arts, Sciences and Humanities, University of Sao Paulo, Av. Arlindo Bettio, 1000, Sao Paulo, SP, 02838-080, Brazil. E-mail: taniaviel@usp.br

Abstract

Aging is a multifaceted process inherent to all living organisms, driven by numerous internal and external factors. Biological aging is marked by the progressive decline of essential physiological processes, leading to tissue integrity loss and cellular function deterioration. This review explores the mechanisms underlying skin aging, emphasizing the role of cellular senescence and its impact on dermal health, with a focus on the senescence-associated secretory phenotype (SASP) and its contribution to systemic inflammation, cancer development and age-related diseases. The effects of UV induced senescence in carcinogenesis is also addressed, relating the oxidative damage caused by prolonged exposure to ultraviolet radiation with the premature acquisition of senescent-like characteristics in cells that ultimately lead to photocarcinogenesis. Furthermore, this review highlights the potential of natural senolytic compounds as a basis for the development of novel treatment options for age related diseases in the skin. *In vitro* research has shown promising results for some natural compounds applied to the treatment of skin diseases. However, many aspects of their use *in vivo* are still unknown. Future research focused on describing the natural compound's interactions on an organism are still needed if these products are ever to be used for the research of new senolytic formulations.

Keywords: Skin cancer, cell senescence, natural products, senolytics, photocarcinogenesis

INTRODUCTION

Aging is a complex process, intrinsic to living organisms, whose course depends on numerous internal and external factors. By definition, biological aging consists of the progressive loss of physiological processes resulting in alterations of tissue integrity and cellular functions (1). This loss of functions occurs due to failures in cellular repair systems, facilitating the occurrence of genetic defects that, in turn, compromise tissues and become more prominent over time. Simultaneously, there is a reduction in mechanisms capable of reducing the proliferation of damaged cells (2,1). These mechanisms include, but are not limited to, apoptosis, autophagy, and cellular senescence and, apparently, occur in different degrees for different cells (1). Cellular senescence is a state of permanent mitotic interruption, which is related to the limitation of tumour progression (3), as well as wound healing and embryonic development. Thus, the cell that has its cycle interrupted does not undergo apoptosis, and acquires a phenotype state known as SASP (senescence-associated secretory phenotype), resulting in the secretion of cytokines, chemokines, metalloproteases, and other proteins that lead to systemic inflammation. This process contributes to the emergence of natural aging characteristics and the development of chronic diseases common in old age (3,4). In this scenario, depending on some environmental factors, skin cells may also suffer the effects of cellular senescence which may contribute to specific aging markers from changes in appearance (wrinkles or fragile skin) to skin cancer (5,6).

The skin is the most exposed organ of our body and is in immediate contact with the environment, suffering direct action from factors such as atmospheric pollution and ultraviolet (UV) radiation, which can cause significant changes in tissues, such as mutations in mitochondrial DNA, reactions with reactive oxygen species (ROS), and shortening of telomeres, thus accelerating aging (5). Throughout the aging process, the components of skin layers tend to undergo senescence (7), with one of the consequences being the reduction in collagen production.

In general, the macroscopic consequences of prolonged exposure to UV radiation manifest visually on human skin in the form of wrinkles, sagging, reduced tensile strength, changes in pigmentation, and, more acutely, hyperchromic spots (5). However, the manifestation of these visual symptoms may indicate more intense damage to fibroblasts that make up the dermal matrix. Fibroblasts are cells capable of creating and maintaining a diverse range of connective tissues rich in extracellular matrix, which ensure the skin's protective and elastic properties (8). As aging progresses, fibroblasts manifest a new phenotype that drastically reduces the volume of proteins produced, with the main consequence of this process being the reduction in the quality of the dermal matrix necessary for the skin to maintain its integrity (5). In addition, this process can be accelerated by contact with UV radiation, which already has the power to cause oxidative damage to DNA due to its relationship with the production of reactive oxygen species (ROS), thus decreasing the dermal matrix's ability to reduce damage and, in more extreme cases, causing photocarcinogenesis (6). Fortunately, in most cases, acute mechanisms of cellular aging come into play before the cell acquires neoplasic characteristics, thus preventing tumor development. Despite this, older adults present failures in the mechanism responsible for the elimination of senescent cells, signalled by secreted cytokines and chemokines (9), a fact that results in the accumulation of these cells in various tissues, such as the intestine, skin, bones, and liver (10). This leads to structural, degenerative, and irreversible damage, as well as fibrosis (1).

Currently, the main way to deal with this undue accumulation of cells in tissues is the use of senotherapeutics, medications capable of attenuating the accumulation of senescent cells in tissues (11). Senotherapeutics are divided into two classes depending on their mechanism of action: senolytics, which kill cells and induce senolysis, and senomorphics, which reduce the production of SASPs, causing senostasis (11). Several drugs with senolytic capacity have already been approved for clinical use, such as glucocorticoids, metformin, rapamycin, quercetin, and navitoclax (12). Despite this, the range of drugs with senotherapeutic characteristics is still very limited. A promising source of new senolytic drugs is those derived from natural products. Agents such as fisetin, quercetin, piperlongumine, and mixed extracts of turmeric are some examples of natural products with potential senolytic action (13). Furthermore, piperlongumine and extracts derived from plants of the genus Solidago are the derivatives of natural products with the greatest action on dermal matrix cells,

thus being an important basis for research on new medications capable of reducing skin senescence.

Concerning this scenario, the aim of this review is to correlate cell senescence and risk for skin cancer, identify potential natural products with senolytic effects and understand how their application can be more efficient through the use of novel research in biotechnology.

SEARCH STRATEGY AND SELECTION CRITERIA

The present project is a literature review with the objective of studying natural products with senolytic capabilities and their effects on the aging process of skin. Bibliographic references were obtained through research in the following data banks: Cochrane, PubMed, Scopus and Scielo utilising the following keywords “Natural Products”, “Senolytics”, “Cellular senescence”, “Dermal Matrix” and “Photocarcinogenesis”. It is worth mentioning that pertinent bibliographic references present in the articles used were also considered in this study.

References selected for this project act in accordance with the following inclusion criteria: qualitative and quantitative research published in English or Portuguese between 2004 and 2024. Works with focus on the aging process of other tissues or articles that do not include information about natural products with senolytic potential were excluded from the research. Finally, the quality control method for the chosen articles was based on metrics used by the data banks in which they were published.

To ease the data extraction of the chosen references, a spreadsheet was made containing the following information: authors, year of publication, study type, methodology used, results, and conclusions. At last, the collected data was synthesized following the main themes of the project and the quality of data evaluated with the aim of accomplishing the study's objectives.

ANALYSIS OF INFORMATION AND DISCUSSION

Cellular Senescence, Aging and Longevity

During the aging process, cells are exposed to senescence-inducing factors (i.e. oxidative stress, telomere shortening, DNA damage, etc.) that are able to induce changes in the individual's morphologic and genetic profile. Cells that undergo this process normally activate a number of metabolic pathways that are responsible for suppressing occasional tumour growth and promoting cell cycle arrest (1). These

responses are triggered mainly by the production of a myriad of pathway mediators that activate the defence mechanisms of a senescent cell, more notably the p53 (cellular tumour antigen), p16 (cyclin-dependent kinase inhibitor) and p21 (pleiotropic cyclin dependent kinase inhibitor) (14) genes, all of which are directly involved in the acquisition of the senescent phenotype. The process begins with the activation of the p53 gene that implies in alteration in gene expression that enables the transcriptional activation of the p21 gene responsible for halting the cellular cycle (14). However, the activation of the pathways related to the p53 and p21 genes is temporary resulting in a decrease in protein levels after the establishment of growth arrest, the lack of these proteins, in turn, activate the expression of the p16 gene which maintains the cell cycle arrest for longer periods of time (14). These changes in metabolism and expression, however, are not entirely related to the acquisition of the senescence-associated secretory phenotype (SASP) as cells that overexpress the p16 and p21 genes develop senescent characteristics but do not secrete any chemicals related to the SASP (15). The acquisition of the phenotype in question is usually related to the presence of cellular damage combined with the aforementioned metabolic changes (15).

All of this seems invasive and unnatural at first, but senescence plays an important role in human aging. Senescence is often categorized as a defence strategy against external or internal stressors (1), as it prevents the proliferation of mutated or malfunctioning cells by locking some cells in a specific stage of the cell cycle (G0). In this state, the cell is not able to duplicate, thus, reducing the occurrence of fibrosis and tumorigenesis (4), all of that while partially maintaining cellular function. The chemokines, cytokines, growth factors and proteases secreted by cells that have acquired the SASP are normally related to primary inflammatory response healing of the affected tissue. However, they are also responsible for warning nearby cells that one of them is senescent, consequently marking it for programmed death (16). Without this process, tumours and defected cells would proliferate in an uncontrolled manner compromising the integrity of the tissue they are part of, ultimately leading to age related diseases such as cancer and organ failure. This mechanism would be perfect for an organism defence if the biological organism were not subject to so many other aging-promoting mechanisms that are subjected to endogenous and exogenous influences, which can determine the course of the aging process, resulting in healthy aging or pathological aging.

Common Pathogenic Mechanisms Underlying Senescence and Cancer

As one gets older, the defence mechanisms of the body will tend to naturally fail in eliminating senescent cells, leading to their accumulation in various tissues and subsequently to organismal senescence (3). This happens mainly because of the aging process of T cells in the immune system, which induces many alterations capable of undermining their objective function of eliminating senescent cells. The induction of this specific phenotype in older T cells provokes the production of pro-inflammatory factors that not only have detrimental effects on immune response but are also capable of stimulating other T cells to become immunologically non-functional (17,18). Immune cells also experience a loss of flexibility in their membranes with aging that can significantly impair their ability to secrete signalling molecules and, mainly, form immune synapses. In turn, this compromises almost all signalling pathways related to the cell's protective functions (19,20,21) ultimately leading to more senescent cells being present in an individual the longer it lives.

Within this context, some works have shown that the induction of cell senescence could be a strategy for cancer treatment. In fact, as cancer cells enter the cellular process of senescence, they would stop the uncontrollable division and the secretion of proteases that attack the cellular matrix leading to the metastatic characteristic of some cancers (22). Paradoxically, cells undergoing senescence may also induce tumour initiation and metastasis through the secretion of SASP-related substances capable of creating the perfect environment for cancer development (22, 23).

These substances are normally associated with inflammation and clearance of senescent cells. However, in greater quantities, they are known for disrupting tissue structure and causing a myriad of age related diseases such as pulmonary hypertension, collagen loss and skin thinning, Alzheimer's disease, Parkinson's disease, osteoarthritis and intervertebral disc degeneration, chronic obstructive pulmonary diseases, emphysema, and many others (3,24,25,26,27,28). More importantly, the SASP related chemicals might also create an immunosuppressant microenvironment that favours malignant transformation and progression depending on the cell type undergoing senescence, the tissue affected as well as the process inducer (22). In other words, even if the cellular arrest caused by senescence impedes the multiplication of malignant cells, the phenotypic change related to this arrest also provokes the secretion of cytokines, chemokines and growth factors that can lead

other cells to tumorigenesis (3, 22). If combined with the loss of function in the immune system related to the process of aging, senescent cells cannot be cleared fast enough to prevent their accumulation in tissues, consequently increasing the production of chemicals responsible for cancer development.

This process is especially evident in skin cancer, as this tissue is constantly exposed to the action of external stressors and can easily be a target for the induction of cellular senescence. Constant exposure, mainly to atmospheric pollution and ultraviolet (UV) radiation, hastens the process of tissue deterioration, causing a myriad of symptoms both macro and microscopically.

Skin, Environamental Factors and Skin Cancer

The skin is the most exposed organ of our body, its main function is to protect our other organs from physical and chemical damage coming from the outside, thus helping maintain our body's homeostasis. Because of this, the skin is constantly bombarded with external stressors that can accelerate aging in its tissues, a process known as extrinsic skin aging (29). Each type of skin aging is associated with different symptoms. Normal aging is related mainly to functional alterations in the cells that compose the dermal matrix, whereas aging provoked by stress is normally characterized by morphologic and physiologic changes that lead to premature aging. Common manifestations of this can appear on skin in the form of wrinkles, solar elastosis and pigment irregularities (5,29). Studies suggest that even though many factors are responsible for inducing extrinsic aging in skin, UV radiation and, in lesser effect, air pollution are the stressors that are able to cause the most damage to the structures of this organ (5,6).

The penetrating properties of UV radiation allows it to interact directly with the dermis layer of the skin thus damaging the fibroblasts that are responsible for maintaining the skin’s dermal matrix. This interaction can cause a variety of adverse effects such as mutations on the cell’s DNA, oxidative damage and telomere shortening all of which provoke the cell into entering a senescence state prematurely (5,7). Senescence in fibroblasts manifest in the form of a phenotype that greatly reduces the amount of proteins produced and secreted by the cell. This lack of extracellular protein present in senescent skin weakens the dermal matrix responsible for keeping the skin’s integrity and function, consequently making it less effective in

keeping the UV radiation from causing age-related diseases and, ultimately, photocarcinogenesis (5,6,29).

UV radiation is capable of induction of carcinogenesis by altering the function of genes responsible for cell growth through mutations in genomic DNA. This process is divided in three stages: initiation, promotion and progression. Even if mutations in the DNA are normally associated with initiating tumorigenesis, these normally remain dormant until exposure to promoting agents that may or may not be carcinogenic themselves, which effectively starts tumour development. Tumour progression, on the other hand, is related to multiple mutations in tumour suppressor genes and oncogenes that are responsible for preventing tumour development (30). UV radiation, however, is a complete carcinogen, meaning it can act as both initiator and promoter in this process, due to the physical differences between UVA and UVB rays. Even though the former is a fairly less efficient carcinogen than the latter, UVA radiation can serve as initiator with UVB serving as promoter in the development of skin cancer (31).

In addition, by applying stress directly to the fibroblasts in the dermis, ultraviolet radiation can lead to skin cancer through the induction of premature senescence leading to senescent cell accumulation (32). This is evident, especially in aged skin, where prolonged *in vitro* exposure to UV radiation induce the acquisition of SASP (33). The presence of this phenotype creates an inflammatory microenvironment that relates to an increase in carcinogenesis in the skin, mainly in the form of carcinomas (34). In other words, the behaviour of SASP-related chemicals in skin is not different from its effects in other tissues, which means that they create an environment that facilitates malignant transformation both by inducing carcinogenesis in healthy cells and by disabling immune clearance of the senescent cells. This process becomes more prominent in aged individuals, since their immune system is already less efficient because of the aging natural process, so the presence of senescent cells and their carcinogenic substances are greatly increased.

The exposure to this specific stressor can also induce metabolic pathways that counteract cellular arrest caused by senescence. Normally, there is a balance between the p53 pathway (responsible for inducing cell cycle arrest) and the AKT/mTOR pro-survival signalling pathway. However, the induction of senescence by UV is capable of shifting the antagonistic balance between the two through the super expression of one of the two pathways (35). This means that if the metabolic balance tips in favour of the AKT/mTOR metabolic pathway, senescent or damaged cells that are currently

under cellular arrest may be pushed back into the cell cycle, thus increasing the probability of malignant transformation because of the increased proliferation of cells that already acquired cancerous properties (35).

Concerning this scenario, it is possible to conclude that UV radiation by itself is capable of inducing and promoting tumour development in skin cells (via induction of cellular senescence), as well as accelerating the aging process of fibroblasts related to photoprotection, consequently weakening the body's natural defences against the stress caused by prolonged exposure to UV light. In tandem, these symptoms promote a vicious cycle of defence inhibition and tumour development, in which a stressor is able to single-handedly create an environment that facilitates tumour growth in this specific tissue.

Spontaneous and drug-induced senescence that promote skin cancer

As described, senescence is a natural process that can also occur without any influence from the environment. The term "inflammaging" refers to the chronic, low-grade inflammation that is related to aging and age-related pathologies, a process that affects various tissues in the body and is characterized by the balance between pro- and anti-inflammatory responses (36). This inflammatory response is caused by the body's natural process of cell clearance, in which small pieces of the destroyed cells called cellular debris still linger in the body's tissues and are recognized by pattern recognition receptors (PRRs), which detect stressed or dying cells and initiate the inflammation related to their degradation. With age, the process of imunnosenescence makes the clearing of the debris less effective, leading to a prolonged exposure to these molecules, progressive activation of PRRs related to immune response and, consequently, to more inflammation (36). Inflammaging is largely related to this imbalance between the production and disposal of cellular debris, characterizing it as an autoimmune process where the immune response of the aging body can harm cells adjacent to the inflammation.

This chronic inflammation can also serve as an internal stressor capable of inducing senescence in other cells. This creates a paradox: inflammaging induces cells into acquiring the SASP, consequently, secreting SASP related chemicals that are related to age related pathologies and propagation of senescence via bystander effect (senescence induced senescence) (36). In turn, since the SASP is regulated similarly as the inflammatory response to other stresses, these senescent cells created via

chronic inflammation contribute to the overall, low grade, general inflammation of tissues (37). Even though the progression of these symptoms can be halted by chemical treatment, in more aggressive pathologies such as cancer, the treatment itself can become a driving factor for senescence.

Drug induced senescence is normally used in oncogenic treatment because of the cell cycle arrest caused by the process. Ideally, this stops tumour progression and leads the way for an effective cycle of chemotherapy. However, several studies have reported that the use of senescence-inducing drugs generates a reversible, drug-resistant state in cells as an acute response to initial treatment (38). Drugs that transiently induce the acquisition of the senescent phenotype more often generate resistant cells. The application of such drugs are associated with an initial phase of cellular death that may seem beneficial in short-term treatment, but negatively influences complementary therapy by creating strands of senescent cells that are resistant against a second phase of drug application (38). Furthermore, drug induced senescent cells are able to bypass the senescence plateau, resuming the cellular cycle and developing into highly tumorigenic cells that, because of the paracrine factors secreted by senescent cells with the SASP, are welcomed to an environment that is beneficial to the growth and development of tumours (39,40). Consequently, drug induced senescence can be detrimental for the long-term treatment of diseases such as cancer, seeing as it cannot fully maintain cell cycle arrest in the cells and induces the selection of drug resistant strands of cells that can possibly become tumours in the future. With this in mind, it is necessary that novel treatments capable of tackling both of these issues be discovered if we ever hope to mitigate the effects of senescence-induced pathologies.

Applying Biotechnology for Skin Cancer treatment

The dichotomy of senescence being both beneficial and detrimental for disease and cancer progression made the use of senescence as a therapeutic factor in cancer treatment uncertain for many years. This, however, changed in the last few years after a series of studies proved that systematically eliminating senescent cells could alleviate the progression of age related diseases or infections as the one caused by Sars-CoV-2 (41,42,43). In this way, it is evident the interest in the development of drugs that can selectively kill these types of cells (the senolytics) in order to combat several diseases, including cancer.

Currently, there are some senolytic drugs that are able to act in skin cancer, two of them being cardiac glycosides and FOX04 peptidomimetics. The former is a natural compound used in cardiology as a cationic inhibitor for Na^+/K^+-ATPase. The inhibition of this metabolic pathway depolarizes the cellular membrane, ultimately provoking apoptosis. Since senescent cells have a bigger concentration of intercellular cations, the effects of the drug in these cells are greater, consequently augmenting the efficiency of the treatment (44,45). The latter is a compound that mimics the FOX04 peptide related to the prevention of apoptosis in senescent cells by sequestering p53 in the nucleus. The synthetic FOX04 competes with the endogenous peptide, provoking the targeted apoptosis of senescent cells by releasing the stored p53 (46). Ultimately, even though there is plenty of research backing these two options of targeted apoptosis for senescent cells, these treatments are normally recommended for use specifically in melanomas. This urges the need for the research and development of a wider variety of efficient options for treating skin cancer, many of which can be found in less researched natural products.

Many natural compounds have been reported to alleviate the development of age related diseases, most of them are potent antioxidants that reduce the oxidative stress suffered by the cells, slowing the aging process. However, there are a few of these compounds that are capable of acting directly in the clearing of senescent cells, making them perfect candidates for the development of novel senolytic drugs (13).

Fisetin is a common flavonoid found in many fruits and vegetables. This substance presents antitumor activity by inhibiting cancer cell proliferation and inducing cancer cell apoptosis in a variety of cell lines, mainly umbilical vein endothelial cells and fibroblasts (47). Even if fisetin is an extremely cell-specific senolytic agent, it proved to be a potent senolytic flavonoid, reducing senescence markers in the tissues that are affected by the presence of this compound (48). Curiously, the anti-proliferative and proapoptotic effects of fisetin were limited to cancer cells, normal cells were much less affected by the treatment, showing good selectivity (49).

Piperlongumine is a biologically active compound extracted from piper plants. This alkaloid has been reported to have wide pharmacological activity, being its anti-cancer characteristics the most well studied of them all (50). Piperlongumine can kill various types of cancer cells including, colon, skin, breast, lung, central nervous system, pancreatic, nasopharyngeal, osseous bladder, prostate, and leukemia with the ability of having selective cytotoxic effects on these cells, and having weak activity

on healthy cells (50,51). For example, piperlongumine was able to suppress skin cancer growth and reduce cell viability by preferentially killing senescent human fibroblasts induced by ionizing radiation without creating more ROS. These effects, however, were mild in normal fibroblasts (50,52). Even though this compound has proven to be effective in preventing cancer development and eliminating senescent cells, its specific targets in the cell are still largely unknown, proving the need to deepen the overall understanding of these compounds.

Solidago virgaurea, commonly known as Goldenrod, is traditionally used in medicine as an anti-inflammatory herbal medicine. Compounds isolated from this plant are reported to have anti-inflammatory, cytotoxic, anti-microbial, anti-mutagenic, anti-oxidative, analgesic and anti-oxidative properties (12). Furthermore, Lämmermannan proved that an alcoholic extract of *Solidago alpestris*, was able to block negative effects of senescence in human skin fibroblasts. The extract was not only able to delay the acquisition of the senescent secretory phenotype, but also preserved the papillary phenotype related to the functionality of human dermal fibroblasts, thus maintaining their ability to stimulate the formation of a full-thickness human skin equivalent (12). At last, the extract was also able to revert the gene expression profile of senescent fibroblasts into one resembling a healthy cell, reducing the expression of various SASP factors and consequently ameliorating the negative effects of the SASP in adjacent cells, mainly the stimulation of pre-neoplasic cell growth. All of this while maintaining the irreversible growth arrest caused by senescence (12).

As is common with most drugs derived from natural products, low bioavailability is a problem that limits the use of some of these compounds as effective treatments for age related diseases in skin. In order to solve this, nanocarriers can be used to deliver these drugs to their targets in a way that makes their therapeutic use more viable (53). Lignin based polymeric nanoparticles (NPs) are a novel technique of creating support structures that uses a natural polymer as its base, lignin grants the NP a high drug loading efficiency, prolonged half-life in the bloodstream, sustained drug release behavior, good bioavailability and tissue permeability, biodegradability, biocompatibility and low toxicity, making it perfect for drug delivery (53). Furthermore, the lignin present in the polymeric NP is also able to act as a UV light blocker acting on wavelengths between 250 and 400nm, thus reducing the effects of UV radiation on skin (54). With this in mind, the use of a lignin based NP to transport one of the natural product based senolytics explained above can not only alleviate the

low bioavailability that limits their use, but also create an environment in which the skin being treated is also protected by a layer of UV blocking structures.

CONCLUSION

This review has provided a comprehensive overview of cellular senescence and its effects on skin aging. Literature indicates that cellular senescence can contribute significantly to the development of age related diseases through different mechanisms, such as reducing collagen production, weakening the dermal matrix responsible for UV protection, SASP related inflammation and oncogenesis. These findings suggest that targeting senescent cells may be a viable strategy for alleviating age-related skin deterioration. Senotherapeutics, especially those derived from natural sources, present a promising new approach to the clearing of senescent cells in human tissues, potentially enhancing long-term skin health and delaying the onset of many age-related conditions.

Despite the extensive research on the effects of senolytic natural extracts in different tissues, there are still some gaps in our understanding of the mechanisms regarding these products. For instance, the substrate interactions and pharmacological synergism of these compounds are not yet fully understood, meaning that the long-term effects of these senotherapeutics on overall aging are still largely unknown. Furthermore, most research conducted focused on this topic relies on *in vitro* models, which may not replicate perfectly their effects on a living organism. Future research should focus on deepening the understanding of how these natural compounds interact with skin cells, investigating the molecular mechanisms behind their pharmacological action may yield important findings on how to better apply natural compounds for the treatment of age-related skin diseases.

In conclusion, the reviewed literature highlights the potential of natural senolytics in addressing skin aging and reducing the development of skin cancer, as well as calling attention to the need for future research on this topic. By filling the existing gaps and exploring new therapeutic avenues, we can advance our understanding and treatment of age-related skin conditions, ultimately improving quality of life for aging populations.

DECLARATION

Author contributions:

Made the bibliographic research and wrote the text: Ramirez, GA;

Made the idea conception and revised the text: Viel, TA.

All authors approved the final version.

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. DODIG, Slavica; ČEPELAK, Ivana; PAVIĆ, Ivan. **Hallmarks of senescence and aging. Biochemia medica,** v. 29, n. 3, p. 483-497, 2019.

2. DILORETO, R.; MURPHY, C. T. The cell biology of aging. **Molecular Biology of the Cell,** v. 26, n. 25, p. 4524–4531, 15 dez. 2015.

3. CAMPISI, J.; ROBERT, L. Cell senescence, role in aging and age-related diseases. **Interdisciplinary topics in gerontology**, v. 39, p. 45–61, 2014.

4. FRANCESCHI C, CAMPISI J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. **J Gerontol A Biol Sci Med Sci.** ;69 Suppl 1:S4-9.2014

5. LAGO, Juliana Carvalh ães; PUZZI, Maria Beatriz. The effect of aging in primary human dermal fibroblasts. **PLoS One,** v. 14, n. 7, p. e0219165, 2019.

6. BAI, B. et al. Intraperitoneally administered biliverdin protects against UVB-induced skin photo-damage in hairless mice. **Journal of Photochemistry and Photobiology B: Biology,** v. 144, p. 35–41, 2015.

7. VICENCIO, J. M. et al. Senescence, Apoptosis or Autophagy? **Gerontology,** v. 54, n. 2, p. 92–99, 2008.

8. PLIKUS, Maksim V. et al. Fibroblasts: Origins, definitions, and functions in health and disease. **Cell,** v. 184, n. 15, p. 3852-3872, 2021.

9. YANAGI, S. et al. The Impacts of Cellular Senescence in Elderly Pneumonia and in Age-Related Lung Diseases That Increase the Risk of Respiratory Infections. **International Journal of Molecular Sciences,** v. 18, n. 3, p. 503–503, 2017.

10. KOROLCHUK, V. I. et al. Mitochondria in Cell Senescence: Is Mitophagy the Weakest Link? **EBioMedicine,** v. 21, p. 7–13, 2017.

11. ZHANG, L. et al. Targeting cellular senescence with senotherapeutics: senolytics and senomorphics. **The FEBS Journal,** v. 290, n. 5, p. 1362–1383, 2022.

12. LÄMMERMANN, Ingo et al. Blocking negative effects of senescence in human skin fibroblasts with a plant extract. **npj Aging and Mechanisms of Disease,** v. 4, n. 1, p. 4, 2018.

13. LI, Wen et al. Emerging senolytic agents derived from natural products. **Mechanisms of ageing and development,** v. 181, p. 1-6, 2019.

14. SHTUTMAN, M. et al. Cellular Model of p21-Induced Senescence. **Methods in Molecular Biology**, p. 31–39, 2016.

15. COPPÉ, J.-P. et al. The Senescence-Associated Secretory Phenotype: The Dark Side of Tumor Suppression. **Annual Review of Pathology: Mechanisms of Disease**, v. 5, n. 1, p. 99–118, 2010.

16. BASISTY, N. et al. A proteomic atlas of senescence-associated secretomes for aging biomarker development. **PLoS biology**, v. 18, n. 1, p. e3000599–e3000599,. 2020.

17. CALLENDER, Lauren A. et al. Human CD 8+ EMRA T cells display a senescence-associated secretory phenotype regulated by p38 MAPK. **Aging cell**, v. 17, n. 1, p. e12675, 2018.

18. WITKOWSKI, Jacek M. et al. Proteodynamics in aging human T cells–The need for its comprehensive study to understand the fine regulation of T lymphocyte functions. **Experimental Gerontology**, v. 107, p. 161-168, 2018.

19. LARBI, Anis et al. Differential role of lipid rafts in the functions of CD4+ and CD8+ human T lymphocytes with aging. **Cellular signalling**, v. 18, n. 7, p. 1017-1030, 2006.

20. FULOP, Tamas et al. Aging, immunosenescence and membrane rafts: the lipid connection. **Longevity & healthspan**, v. 1, p. 1-9, 2012.

21. FULOP, Tamas et al. Cellular signaling in the aging immune system. **Current opinion in immunology**, v. 29, p. 105-111, 2014.

22. FAGET, Douglas V.; REN, Qihao; STEWART, Sheila A. Unmasking senescence: context-dependent effects of SASP in cancer. **Nature Reviews Cancer**, v. 19, n. 8, p. 439-453, 2019.

23. SCHMITT, Clemens A.; WANG, Boshi; DEMARIA, Marco. Senescence and cancer—role and therapeutic opportunities. **Nature reviews Clinical oncology**, v. 19, n. 10, p. 619-636, 2022.

24. BITTO, Alessandro et al. Stress-induced senescence in human and rodent astrocytes. **Experimental cell research**, v. 316, n. 17, p. 2961-2968, 2010.

25. CAMPISI, Judith. Aging, cellular senescence, and cancer. **Annual review of physiology**, v. 75, p. 685-705, 2013.

26. NOUREDDINE, Hibo et al. Pulmonary artery smooth muscle cell senescence is a pathogenic mechanism for pulmonary hypertension in chronic lung disease. **Circulation research**, v. 109, n. 5, p. 543-553, 2011.

27. ROBERTS, S. et al. Senescence in human intervertebral discs. **European Spine Journal**, v. 15, p. 312-316, 2006.

28. SALMINEN, Antero et al. Astrocytes in the aging brain express characteristics of senescence-associated secretory phenotype. **European Journal of Neuroscience**, v. 34, n. 1, p. 3-11, 2011.

29. VIERKÖTTER, Andrea; KRUTMANN, Jean. Environmental influences on skin aging and ethnic-specific manifestations. **Dermato-endocrinology**, v. 4, n. 3, p. 227-231, 2012.

30. SOEHNGE, Holly; OUHTIT, Allal; ANANTHASWAMY, O. N. Mechanisms of induction of skin cancer by UV radiation. **Front Biosci**, v. 2, n. 1, p. 538-51, 1997.

31. KANJILAL, S.; ANANTHASWAMY, H. N. Molecular biology of skin carcinomas. **Basal and squamous cell skin cancers of the head and neck. Eds: Weber R., Miller M., Goepfert H., Williams and Wilkins, Baltimore**, p. 25-26, 1996.

32. GHOSH, Kanad; CAPELL, Brian C. The senescence-associated secretory phenotype: critical effector in skin cancer and aging. **Journal of Investigative Dermatology**, v. 136, n. 11, p. 2133-2139, 2016.

33. SHIN, J.; KIM, J.-H.; KIM, E. K. Repeated exposure of human fibroblasts to UVR induces secretion of stem cell factor and senescence. **Journal of the European Academy of Dermatology and Venereology**, v. 26, n. 12, p. 1577-1580, 2012.

34. WONG, Christine E. et al. Inflammation and Hras signaling control epithelial–mesenchymal transition during skin tumor progression. **Genes & development**, v. 27, n. 6, p. 670-682, 2013.

35. STROZYK, Elwira; KULMS, Dagmar. The role of AKT/mTOR pathway in stress response to UV-irradiation: implication in skin carcinogenesis by regulation of apoptosis, autophagy and senescence. **International journal of molecular sciences**, v. 14, n. 8, p. 15260-15285, 2013.

36. FRANCESCHI, Claudio et al. Inflammaging and 'Garb-aging'. **Trends in Endocrinology & Metabolism**, v. 28, n. 3, p. 199-212, 2017.

37. FREUND, Adam et al. Inflammatory networks during cellular senescence: causes and consequences. **Trends in molecular medicine**, v. 16, n. 5, p. 238-246, 2010.

38. ACHUTHAN, Santhi et al. Drug-induced senescence generates chemoresistant stemlike cells with low reactive oxygen species. **Journal of Biological Chemistry**, v. 286, n. 43, p. 37813-37829, 2011.

39. RADISKY, D. C. et al.. Rac1b and reactive oxygen species mediate MMP-3-induced EMT and genomic instability. ***Nature***, *436*(7047), 123-127, 2005.

40. SHARMA, S. V. et al A chromatin-mediated reversible drug-tolerant state in cancer cell subpopulations. ***Cell***, *141*(1), 69-80, 2010.

41. BAKER, D. J. et al. Naturally occurring p16Ink4a-positive cells shorten healthy lifespan. **Nature**, v. 530, n. 7589, p. 184–189, 2016.

42. CHILDS, B. G., et al. Senescent intimal foam cells are deleterious at all stages of atherosclerosis. **Science** 354.6311472-477. 2016

43. VIEL, T.A. et al. Microdose lithium reduces cellular senescence in human astrocytes - a potential pharmacoterapy for COVID-19? **Aging (Albany NY)** v. 12, n. 11, p. 10035-10040, 2020.

44. GUERRERO, A. et al. Cardiac glycosides are broad-spectrum senolytics. **Nature metabolism**, v. 1, n. 11, p. 1074–1088, 2019.

45. TRIANA-MART ÍNEZ, F. et al. Identification and characterization of Cardiac Glycosides as senolytic compounds. Nature communications, v. 10, n. 1, 2019.

46. BAAR, M. P. et al. Targeted Apoptosis of Senescent Cells Restores Tissue Homeostasis in Response to Chemotoxicity and Aging. **Cell**, v. 169, n. 1, p. 132-147.e16, 2017.

47. KASHYAP, D. et al. Fisetin: A bioactive phytochemical with potential for cancer prevention and pharmacotherapy. **Life sciences**, v. 194, p. 75–87, 2018.

48. ZHU, Y. et al. New agents that target senescent cells: the flavone, fisetin, and the BCL-XL inhibitors, A1331852 and A1155463. **Aging**, v. 9, n. 3, p. 955–963, 2017.

49. LALL, R. K.; VAQAR MUSTAFA ADHAMI; MUKHTAR, H. Dietary flavonoid fisetin for cancer prevention and treatment. **Molecular nutrition & food research**, v. 60, n. 6, p. 1396–1405, 2016.

50. BEZERRA, D. P. et al. Overview of the therapeutic potential of piplartine (piperlongumine). **European journal of pharmaceutical sciences**, v. 48, n. 3, p. 453–463, 2013.

51. KAMIL PISKA et al. Piperlongumine (piplartine) as a lead compound for anticancer agents – Synthesis and properties of analogues: A mini-review. **European journal of medicinal chemistry**, v. 156, p. 13–20, 2018.

52. WANG, Y. et al. Discovery of piperlongumine as a potential novel lead for the development of senolytic agents. **Aging**, v. 8, n. 11, p. 2915–2926, 2016.

53. LIU, Kefeng, et al. Development of novel lignin-based targeted polymeric nanoparticle platform for efficient delivery of anticancer drugs. **ACS Biomaterials Science & Engineering,** p.1730-1737, 2018.

54. HASAN SADEGHIFAR; RAGAUSKAS, A. Lignin as a UV Light Blocker—A Review. **Polymers,** v. 12, n. 5, p. 1134–1134, 2020.