A deep dive into the orchard of health: Exploring the anti-cancer and anti-aging potential of apple polyphenols

Li-Ching Chen [a], Han-Sheng Chang [a], Yuan-Soon Ho [b,*]

[a] Department of Biological Science & Technology, College of Life Sciences, China Medical University, Taichung, Taiwan
[b] Institute of Biochemistry and Molecular Biology, College of Life Sciences, China Medical University, Taichung, Taiwan

Abstract

Apples, a ubiquitous and beloved fruit, harbor a treasure trove of bioactive compounds, with apple polyphenols (APs) taking center stage. This review delves into the latest scientific advancements illuminating the anti-cancer and anti-aging properties of APs. We dissect the intricate mechanisms by which APs combat cancer initiation, progression, and metastasis, highlighting their prowess in inducing apoptosis, inhibiting angiogenesis, and modulating cell signaling pathways. Furthermore, we explore the multifaceted ways APs combat aging, including their potent antioxidant and anti-inflammatory actions, DNA protective effects, and ability to modulate cellular processes like autophagy and metabolism. This comprehensive review underscores the therapeutic promise of APs in promoting healthy aging and combating age-related diseases like cancer.

Keywords: Anti-cancer, Anti-inflammatory, Apple polyphenols, Autophagy, DNA protection

1. Unveiling the powerhouse within the apple

The saying that consuming an apple daily contributes to maintaining good health aligns with scientific evidence, as apples are progressively acknowledged for their exceptional nutritional and health-promoting properties. Beyond their nutritional value, apples are abundant in bioactive compounds, with apple polyphenols (APs) garnering significant attention for their potent antioxidant, anti-inflammatory, anti-cancer, and anti-aging properties. This review delves into the latest scientific breakthroughs unraveling the multifaceted mechanisms by which APs combat cancer and aging, highlighting their potential as promising therapeutic agents for promoting human health (see Table 1).

2. A glimpse into the chemical diversity of APs

APs are an umbrella term for several phenolic compounds with various biological activities. A comparison of polyphenol levels reveals apples contain 110–220 mg per 100 g [1], with the peel richest in quercetin, catechin, and chlorogenic acid [2]. Pomegranate juice leads with 680–700 mg per 100 mL [3], followed by blueberry (520–550 mg) [4] and orange juice (75–85 mg) [3]. While dark berries surpass apples in total polyphenols, apples are notable for their high quercetin content and distinct health benefits [2]. Despite lower levels and losses during processing, their unique profile and availability make them a key source of polyphenols.

Here are the main chemical components of APs:

2.1. Flavonoids

Quercetin is a potent antioxidant known for its anti-inflammatory, antiviral, and anticancer properties. Quercetin, a flavonoid with potential health benefits, has been studied for its effective dosage in preventive healthcare. Research suggests a recommended daily dosage of 500–1000 mg, divided into

Received 1 August 2024; accepted 17 January 2025.
Available online 31 March 2025

* Correspondence author at: Institute of Biochemistry and Molecular Biology, College of Life Sciences, China Medical University, No. 100, Sec. 1, Jingmao Rd., Beitun Dist., Taichung City 406040, Taiwan.
E-mail address: hoyuansn@mail.cmu.edu.tw (Y.-S. Ho).

https://doi.org/10.38212/2224-6614.3539

Table 1. Summary of the anti-cancer and anti-aging effects of APs.

Category	Model	Compounds effects
Flavonoids		
Quercetin	Aging male C57BL/6 mice	Co-treatment with quercetin and dasatinib can effectively promote the expression of p16, p21, and p16 proteins in perigonadal white adipose tissue while slowing down the expression of related β-galactosidase enzymes and pro-inflammation genes (mcp1, tnf-α, il-1α, il-1β, il-6, cxcl2, and cxcl10) in aging cells [81].
Kaempferol	PANC-1 Mia PaCa-2	Kaempferol regulates Akt/mTOR activity by inhibiting transglutaminase (TGM2) in pancreatic cancer cells, thereby inducing ROS-mediated apoptosis [82].
Catechins Epicatechins	MIAPaCa-2 SU 86.86	Catechin derivatives serve as covalent inhibitors of the p65 subunit of NF-κB, thereby inhibiting the expression of MMP9, MMP2, cMyc, and BCL-2 genes in pancreatic cancer cells [83].
Phenolic acids		
Chlorogenic acid	MCF-7	Chlorogenic acid blocks the Epithelial-mesenchymal transition by inhibiting LRP6 protein, thereby upregulating epithelial protein markers (E-cadherin and ZO-1) and downregulating mesenchymal protein markers (ZEB1, N-cadherin, vimentin, snail, and slug) to alleviate breast cancer cell metastasis and invasion ability [10].
Caffeic acid	PC-3 C4-2B	Caffeic acid treatment effectively inhibits HRAS, RAF1, AKT2, GSK3A, and EGF gene expression and EGFR (Y845, Y1069, Y1148, Y1173), FAK, Akt, and ERK1/2 protein phosphorylation in pancreatic cancer cells [84].
Dihydrochalcones		
Phlorizin	HepG2	Phlorizin effectively inhibits the activity of DNA topoisomerases IIα in liver cancer cells, causing G0/G1 cell cycle arrest. This inhibits cancer cell proliferation and promotes cell apoptosis. In addition, Phloridzin effectively reduces mitochondrial membrane potential and ATP levels in liver cancer cells [85].
Tannins		
Condensed tannins	TFK-1	Condensed tannins treatment effectively inhibits the expression of cyclin E and the cdc25a protein and promotes cytochrome c, caspase-3, and caspase-8, thereby causing G2/M cell cycle arrest and inducing cell apoptosis [86].
Anthocyanins		
Cyanidin	MCF-7	Cyanidin treatment effectively promotes p53, Bax, Caspase3, CYP1, and CYP2 gene expression and inhibits Bcl2 gene expression, thereby promoting cell apoptosis in breast cancer cells [87].

two doses of 250−500 mg each, taken twice daily for optimal results [5]. Its ability to combat oxidative stress and reduce inflammation makes it a valuable compound in the field of health and nutrition. Additionally, its potential in fighting viral infections and inhibiting the growth of cancer cells has garnered significant interest in the scientific community. Kaempferol is a flavonoid praised for its potential health benefits, including anticancer properties by inhibiting cancer cell growth and inducing cell death [6]. Its antioxidant effects protect cells from oxidative damage, potentially lowering chronic disease risk. Additionally, kaempferol exhibits anti-inflammatory properties that are beneficial for managing inflammation [7]. Catechins and epicatechins [8], known for their strong antioxidant and anti-cancer effects, are crucial for cardiovascular health. Research indicates they shield the heart and blood vessels from damage and enhance overall heart function.

2.2. Phenolic acids

Chlorogenic Acid is a naturally occurring compound that is primarily found in coffee and also commonly present in apples [9]. This compound is known for its antioxidant, anti-inflammatory, and hypoglycemic effects. Research has shown that Chlorogenic Acid has the potential to provide various health benefits, making it an area of interest for further study and exploration. Its ability to combat oxidative stress [10], reduce inflammation, and lower blood sugar levels makes it a promising compound for potential therapeutic applications. Caffeic acid, renowned for its antioxidant and anti-inflammatory properties [11], is valuable for safeguarding cells against oxidative damage. Neutralizing free radicals and reducing inflammation promotes overall health. Research indicates caffeic acid's potential benefits for various health conditions, marking it as a promising natural medicine subject.

2.3. Dihydrochalcones

Phlorizin is recognized for its anti-diabetic properties, as it effectively inhibits glucose absorption in the body [11]. Phlorizin, a plant-derived glycoside, is generally recommended for blood sugar management within 400–800 mg daily. Depending on individual needs and clinical guidance, the suggested treatment duration typically spans 8–12 weeks [12]. Additionally, it is known for its antioxidant and anti-inflammatory effects. These properties make Phlorizin a promising candidate for potential therapeutic applications in managing diabetes and related complications.

2.4. Tannins

Condensed tannins, a type of polyphenol, are renowned for their antioxidant [13], and antiviral properties. Research suggests they may help fight oxidative stress [14], inhibit harmful bacteria growth, and combat viral infections, making them valuable in natural health and wellness. Tannins are known for their antioxidant properties, which can provide various health benefits. The recommended dosage for tannins ranges from 500 to 1500 mg per day, with a suggested duration of use spanning 4–12 weeks for optimal results [15].

2.5. Anthocyanins

Anthocyanins, a group of naturally occurring pigments found in various plant sources, have been studied for their potential health benefits. Research suggests an effective daily dosage of 100–300 mg for optimal results. Key dietary sources of anthocyanins include dark-colored berries, grapes, and purple cabbage, as highlighted in studies such as those by Wallace et al. (2016) [16]. Cyanidin is a class of pigments known for imparting red, purple, and blue hues to various fruits and apples [17]. These pigments are responsible for the vibrant colors found in nature and possess potent antioxidant and anti-inflammatory properties. Studies have shown that cyanidin can help combat oxidative stress and reduce inflammation, making it a valuable component of a healthy diet. Its presence in various plant-based foods underscores the importance of consuming diverse colorful produce to benefit from its protective effects.

These compounds work together to give APs significant health benefits in terms of antioxidant, anti-inflammatory, anti-cancer, and anti-aging. Each compound's specific structure and function can be further investigated to reveal its specific mechanism of action in different biological processes.

3. APs: unleashing their anti-cancer arsenal (Fig. 1)

Cancer, a prominent contributor to global mortality rates, is characterized by the unregulated proliferation and dissemination of abnormal cells. Antineoplastic agents, known for their efficacy in combating cancer, can target multiple stages of carcinogenesis, encompassing initiation, promotion, and progression.

3.1. Quenching the flames of oxidative stress: the antioxidant powerhouse

Oxidative stress, an imbalance between reactive oxygen species (ROS) production and antioxidant defense, is implicated in cancer development. APs, mainly flavonoids and phenolic acids, act as potent antioxidants, scavenging free radicals and protecting cells from oxidative damage [18]. The mechanism of action of APs involves donating electrons to neutralize free radicals, thereby halting the chain reaction of oxidative damage [19]. This process effectively mitigates the harmful effects of oxidative stress on the body. By interrupting the propagation of free radicals, APs play a crucial role in maintaining cellular health and function. This mechanism underscores the potential health benefits of consuming APs, highlighting their importance in promoting overall well-being. They also upregulate endogenous antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), bolstering the body's natural defense system. Numerous *in vitro* and *in vivo* studies have provided scientific evidence demonstrating the potent antioxidant activity of APs. For example, research has shown that apple peel extract, rich in quercetin and chlorogenic acid, is highly effective in scavenging free radicals [20] and protecting DNA from oxidative damage in human colon cancer cells [21]. These findings highlight the potential health benefits of APs and their role in combating oxidative stress at the cellular level.

3.2. Halting the engine of cancer: inhibiting cell proliferation

Uncontrolled cell proliferation is a well-established hallmark of cancer. Research has shown that APs possess notable anti-proliferative effects [22],

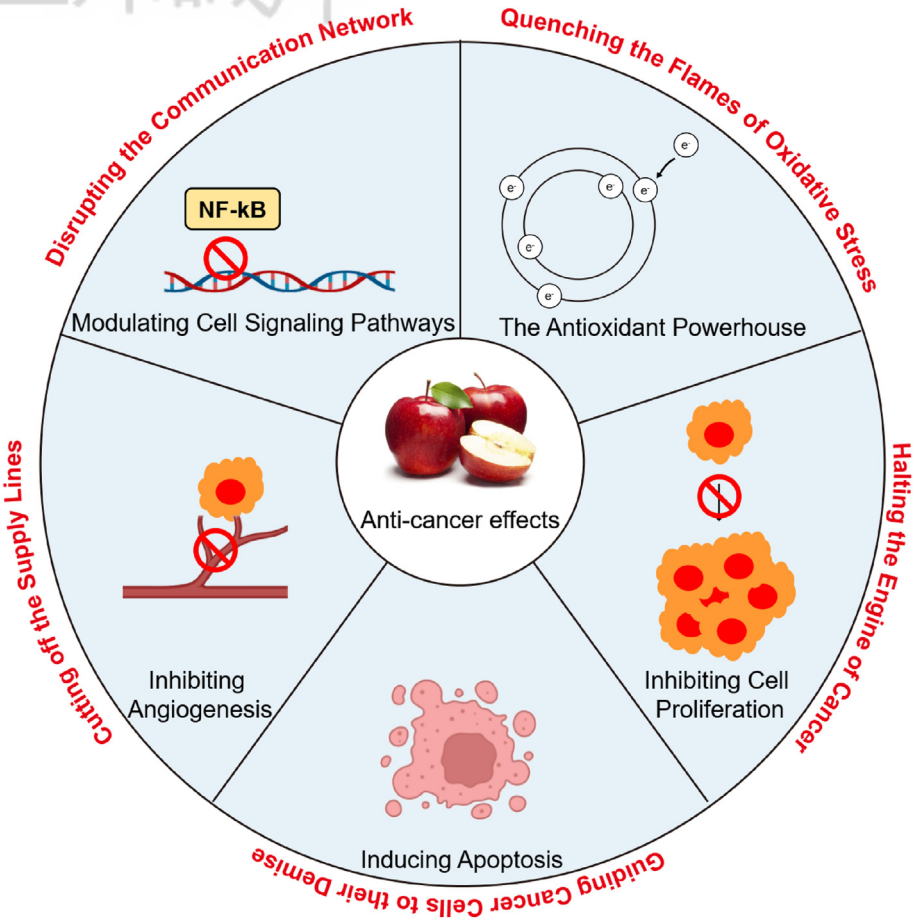

Fig. 1. The mechanism for APs involves various anti-cancer actions. Firstly, they act as a potent antioxidant, quenching oxidative stress and reducing cellular damage. Additionally, they halt cancer progression by inhibiting cell proliferation and guiding cancer cells towards apoptosis, or programmed cell death. Furthermore, APs inhibit angiogenesis, the formation of new blood vessels that supply tumors with nutrients. Lastly, they disrupt cell signaling pathways, impeding the communication network that promotes cancer growth. These multi-faceted actions make APs a promising candidate for cancer prevention and treatment. Figure was created with BioRender software (https://biorender.com/).

effectively impeding the growth of cancer cells. This discovery holds significant promise for developing therapeutic interventions targeting cancer cell proliferation. The mechanism of action of APs involves targeting multiple signaling pathways crucial for cell cycle regulation [23]. By doing so, they can induce cell cycle arrest and effectively inhibit the proliferation of cancer cells [24]. This multi-faceted approach makes APs a promising candidate for potential therapeutic interventions to combat cancer.

For example, APs have been shown to effectively downregulate cyclin-dependent kinases (CDKs), which are critical regulators of cell cycle progression [25]. This regulatory action plays a crucial role in controlling cell growth and division. By targeting CDKs, APs have the potential to modulate cell cycle dynamics and inhibit uncontrolled cell proliferation [23]. This mechanism of action highlights the potential of APs as a natural compound for regulating cell cycle progression and potentially impacting various cellular processes. To inhibit cell cycle progression, it is essential to upregulate cyclin-dependent kinase inhibitors (CDKIs) responsible for blocking CDK activity. Additionally, the induction of tumor suppressor genes by apple extract, such as p53 [26], plays a crucial role in regulating cell cycle arrest and promoting apoptosis. These mechanisms are vital in maintaining the balance of cell proliferation and preventing uncontrolled growth, ultimately contributing to the suppression of tumor development. Several studies have provided scientific evidence indicating that apple peel extract can hinder the growth of different cancer cell lines, such as those found in breast [27], colon [28], lung [29], and prostate cancer. One study, for example, demonstrated that apple peel extract containing high levels of procyanidins effectively suppressed the proliferation of human breast cancer cells by causing cell cycle arrest and stimulating apoptosis [30]. This

suggests that apple peel extract may have potential as a natural compound for cancer treatment.

3.3. Guiding cancer cells to their demise: inducing apoptosis

Apoptosis, also known as programmed cell death, is a highly regulated biological process for removing damaged or unnecessary cells. In the cancer context, the apoptosis evasion by cancer cells plays a significant role in promoting tumor growth and survival. However, advancements in apoptotic agents (APs) have shown promise in reactivating apoptotic pathways within cancer cells, ultimately leading to their demise. This ability to target and induce apoptosis in cancer cells presents a potential avenue for therapeutic intervention in cancer treatment.

The mechanism of action of APs involves the induction of apoptosis through both intrinsic (mitochondrial-mediated) [31] and extrinsic (death receptor-mediated) pathways [32]. This process ultimately leads to programmed cell death, highlighting the potential therapeutic implications of APs in targeting aberrant cell growth and survival. The mechanism by which they achieve this involves increasing the expression of pro-apoptotic proteins [33], such as Bax, Bak, and caspase-3, while concurrently decreasing the expression of anti-apoptotic proteins like Bcl-2 and Bcl-xL [34]. This modulation of protein expression ultimately promotes the initiation and execution of apoptosis, contributing to the regulation of cell death.

Activation of death receptors such as Fas and TRAIL receptors [35] by apoptosis inducers has been the subject of scientific study. Research has demonstrated that APs can induce apoptosis in various cancer cell lines, including leukemia, melanoma, and colon cancer cells. For example, a study found that apple juice concentrate rich in polyphenols induced apoptosis in human leukemia cells [36] by activating caspase-3 and cleaving PARP, which are key executioners of the apoptosis process. These findings highlight the potential of APs in targeting specific receptors to trigger programmed cell death in cancer cells.

3.4. Cutting off the supply lines: inhibiting angiogenesis

Angiogenesis, forming new blood vessels, plays a crucial role in tumor growth and metastasis. A class of compounds known as APs has been found to possess anti-angiogenic properties [37], effectively disrupting the blood supply to tumors. This disruption ultimately leads to the starvation of tumors, inhibiting their growth and spread. The ability of APs to target the blood vessels that support tumor growth holds promise for developing new anti-cancer therapies. The mechanism of action of APs involves the inhibition of angiogenesis through the downregulation of pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) [37]. By targeting these key factors, APs effectively hinder the process of angiogenesis, which is crucial for the growth and spread of new blood vessels. This mechanism demonstrates the potential of APs as a promising approach to combating diseases and conditions characterized by excessive angiogenesis, such as cancer and certain inflammatory disorders. Inhibiting the activity of matrix metalloproteinases (MMPs) is crucial for preventing the degradation of the extracellular matrix, which is essential for the formation of new blood vessels. By targeting these enzymes, APs can effectively regulate the process of angiogenesis and potentially impact various physiological and pathological conditions [38]. This inhibition may offer promising therapeutic opportunities for conditions such as cancer, cardiovascular diseases, and inflammatory disorders, where abnormal angiogenesis plays a significant role. Based on scientific evidence, it has been established that APs can inhibit angiogenesis in various experimental models. Notably, studies have demonstrated that apple procyanidins can effectively impede VEGF-induced angiogenesis in human umbilical vein endothelial cells (HUVECs) [37,39], commonly used as a model for studying angiogenesis. This evidence underscores the potential of APs to modulate angiogenesis and suggests avenues for further exploration in this area of research.

3.5. Disrupting the communication network: modulating cell signaling pathways

Cancer cells can manipulate normal cell signaling pathways to enhance their survival and growth and spread to other body parts. By utilizing this strategy, cancer cells can disrupt the intricate communication network responsible for driving the progression of the disease. As a result, it is essential to explore the potential of APs in modulating these pathways, as they can interfere with the mechanisms that facilitate cancer advancement.

The mechanism of action of APs involves targeting multiple signaling pathways implicated in cancer development. One such pathway is the nuclear factor-kappa B (NF-κB) pathway, which is crucial in regulating inflammation, cell survival, and

metastasis. APs have been shown to inhibit the activation of NF-κB [40,41], impacting these critical cellular processes in cancer progression. This multifaceted approach highlights the potential of APs as a promising therapeutic option for combating cancer. The other pathway is the mitogen-activated protein kinase (MAPK) pathway, which regulates cell proliferation, differentiation, and apoptosis. APs modulate the MAPK signaling [41], thereby influencing these fundamental cellular processes. Phosphatidylinositol 3-kinase (PI3K)/Akt pathway: APs inhibit the PI3K/Akt pathway, a significant driver of cell survival and growth. Based on scientific evidence, numerous studies have demonstrated that APs can modulate signaling pathways in different cancer cell lines. This modulation ultimately results in decreased proliferation, increased apoptosis, and reduced metastasis. These findings highlight the potential of APs as a promising approach to cancer treatment and warrant further investigation into their therapeutic benefits.

4. APs: turning back the clock on aging (Fig. 2)

Aging is a natural biological phenomenon marked by a gradual deterioration in bodily functions, heightened vulnerability to chronic ailments, and eventual mortality. Although aging is not classified as a disease in itself, it significantly increases the risk of developing a range of age-related conditions such as cancer [42,43], cardiovascular disorders [44], neurodegenerative diseases [45], and metabolic disorders [46]. Advanced therapeutics known as APs have demonstrated potent capabilities as anti-aging interventions by targeting multiple aging indicators and fostering extended longevity.

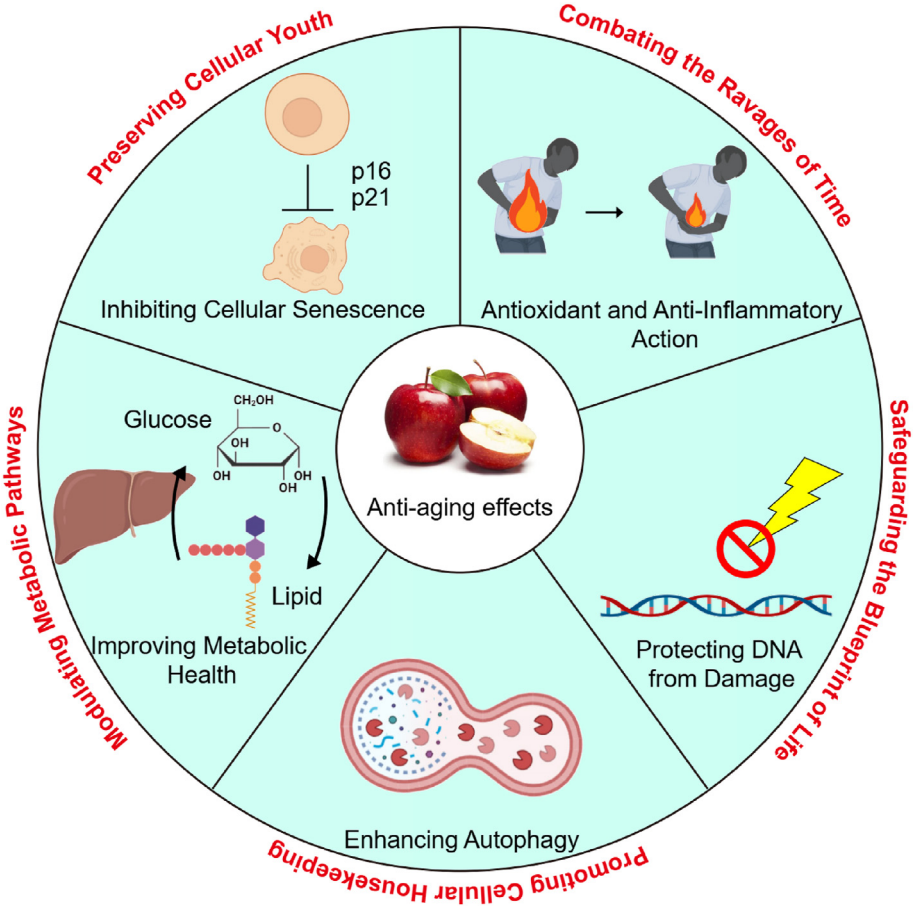

Fig. 2. Our current understanding of the mechanism for APs: Turning Back the Clock on Aging, as depicted in this figure, encompasses several key aspects. Firstly, the polyphenols exhibit antioxidant and anti-inflammatory actions, effectively combating the ravages of time on cellular health. Secondly, they play a crucial role in safeguarding the blueprint of life by protecting DNA from damage. Furthermore, these polyphenols promote cellular housekeeping by enhancing autophagy, the process by which cells remove damaged components. Lastly, they contribute to preserving cellular youth by inhibiting cellular senescence, thereby maintaining the vitality and functionality of cells. Overall, the multifaceted mechanisms of APs hold promise for mitigating the effects of aging on a cellular level. Figure was created with BioRender software (https://biorender.com/).

4.1. Combating the ravages of time: antioxidant and anti-inflammatory action

Oxidative stress and chronic inflammation are recognized as significant contributors to the aging process and the development of age-related diseases. Antioxidant compounds, such as APs, have been shown to possess potent antioxidant [18] and anti-inflammatory [47] properties, which play a crucial role in combating these detrimental processes. As a result, APs have the potential to effectively mitigate the impact of oxidative stress and chronic inflammation on aging and age-related diseases. The mechanism of action of antioxidant compounds involves scavenging free radicals [48], upregulating antioxidant enzymes [49], and inhibiting pro-inflammatory pathways. This effectively reduces oxidative stress and inflammation within the body. Scientific evidence supports the protective effects of APs against age-related oxidative damage and inflammation in multiple tissues, such as the brain, heart, and liver. Research studies have demonstrated that APs can improve cognitive function and decrease oxidative stress in aged mice [50] and in clinical trials [51,52] indicating their potential benefits in counteracting age-related physiological decline. These findings highlight the promising role of APs as a natural intervention to mitigate the impact of aging on various organ systems.

4.2. Safeguarding the blueprint of life: protecting DNA from damage

DNA damage is a significant factor in the processes of cellular senescence, aging, and the development of cancer. APs have been found to possess DNA protective effects, playing a crucial role in safeguarding the integrity of our genetic material. This highlights the potential importance of APs in mitigating the impact of DNA damage and its associated consequences.

The mechanism of action of APs involves protecting DNA from oxidative damage, UV radiation [53], and other environmental toxins [54]. This protection is essential in maintaining the integrity of genetic material and preventing potential mutations that could lead to adverse health effects. By shielding DNA from these harmful factors, APs play a crucial role in preserving the stability and functionality of genetic material within cells. This mechanism of action highlights the importance of APs in safeguarding cellular health and overall well-being. Based on current research, it has been found that the APs direct scavenging of free radicals and the prevention of DNA strand breaks are crucial in maintaining cellular health [55]. Additionally, evidence suggests that enhancing DNA repair mechanisms by APs is essential for overall DNA integrity [56]. These processes play a significant role in protecting against potential DNA damage and maintaining genetic stability. Modulating cell cycle checkpoints to allow time for DNA repair is crucial to maintaining genomic stability. Scientific evidence has demonstrated that certain compounds, such as APs, can protect DNA from damage induced by various agents, including hydrogen peroxide and UV radiation [57]. By leveraging the protective properties of APs, it may be possible to manipulate cell cycle checkpoints to allow sufficient time for DNA repair processes. This approach holds promise for enhancing the cell's ability to maintain genomic integrity and ultimately contribute to overall cellular health.

4.3. Promoting cellular housekeeping: enhancing autophagy

Autophagy is a fundamental cellular mechanism responsible for the breakdown and renewal of impaired cellular constituents. Its significance lies in maintaining cellular equilibrium and preventing the build-up of dysfunctional proteins and organelles, which are linked to the aging process and age-related ailments. The mechanism of action of APs involves enhancing autophagy through several key processes [58]. Firstly, they activate important autophagy-related proteins such as LC3 and Beclin-1 [59], which play crucial roles in the initiation and progression of autophagy. Additionally, APs inhibit the mTOR pathway [31], a negative autophagy regulator, promoting autophagy induction. Furthermore, APs facilitate the formation of autophagosomes, the key structures involved in the sequestration of cellular components for degradation, and promote their fusion with lysosomes, where the degradation process occurs. Overall, these actions collectively contribute to the enhancement of autophagy by APs. Based on scientific evidence, it has been established that autophagy is promoted by APs in various cell types, such as neurons, hepatocytes, and cardiomyocytes [60]. For instance, studies have illustrated that apple polyphenol extract enhances autophagy in mouse hepatocytes, improving liver function [61] and reducing oxidative stress. Similarly, phloridzin has been found to induce autophagy in human cardiomyocytes [62], thereby offering protection against oxidative damage. These findings underscore the potential of APs in modulating autophagy and their potential therapeutic implications for various health conditions.

4.4. Modulating metabolic pathways: improving metabolic health

Metabolic dysfunction is a well-established characteristic of aging and is closely linked to a range of age-related conditions such as diabetes, obesity, and cardiovascular disease [46,63]. Research has indicated that APs play a role in enhancing metabolic health by influencing important metabolic pathways. The mechanism of action of APs involves several key processes that contribute to improving metabolic health. Firstly, APs enhance insulin sensitivity [64] and promote the uptake of glucose, which is essential for maintaining proper blood sugar levels. Additionally, they modulate lipid metabolism, helping reduce lipids accumulation within the body [58,65]. Furthermore, APs activate AMP-activated protein kinase (AMPK) [66], a crucial regulator of energy homeostasis that plays a central role in maintaining metabolic balance. These combined effects contribute to the overall improvement of metabolic health and function.

Recent scientific studies have provided evidence that demonstrates the positive impact of APs on metabolic health in both animal models and human subjects. For example, research has shown that apple polyphenol extract can enhance insulin sensitivity and lower blood glucose levels in diabetic mice. Additionally, studies have indicated that phloridzin has the potential to decrease lipid accumulation and improve lipid metabolism in obese mice. These findings suggest promising benefits of APs in improving metabolic health, highlighting the potential for further exploration in human subjects.

4.5. Preserving cellular youth: inhibiting cellular senescence

Cellular senescence is a state of irreversible cell cycle arrest that contributes to aging and age-related diseases. Senescent cells secrete pro-inflammatory cytokines, growth factors, and proteases, collectively known as the senescence-associated secretory phenotype (SASP), which can promote tissue dysfunction and chronic inflammation. The mechanism of the action of APs involves inhibiting cellular senescence through several key processes. Firstly, APs reduce oxidative stress and DNA damage, known triggers of senescence within cells [67]. Additionally, APs modulate the expression of senescence-associated genes such as p16INK4a and p21 [57], further contributing to the inhibition of cellular senescence. Furthermore, APs phloretin inhibits the SASP [68] and reduces chronic inflammation [69], both associated with the senescent state. Overall, the multifaceted action of APs effectively inhibits cellular senescence and its associated detrimental effects. Scientific evidence shows that certain active compounds, such as quercetin and apple polyphenol extract, can inhibit cellular senescence in various cell types [70], including fibroblasts [70], endothelial cells [71], and immune cells. For instance, studies have indicated that quercetin can effectively reduce oxidative stress and inhibit senescence in human fibroblasts [70]. These findings suggest the potential of these active compounds in mitigating cellular senescence and its associated effects.

5. Potential clinical applications and future directions

The evidence substantiating APs' anti-cancer and anti-aging properties lays a strong foundation for their potential clinical utilization. Nevertheless, several obstacles and future avenues need to be navigated to fully exploit their therapeutic benefits.

5.1. Challenges and limitations

Enhancing the bioavailability of APs presents a significant challenge due to their extensive metabolism and degradation within the gastrointestinal tract [71,72]. To improve their bioavailability, it is imperative to investigate various strategies, including encapsulation [73] and formulation with bio-enhancers. These approaches warrant further exploration to address this critical issue. Standardization is crucial for APs due to the potential variations in concentration and composition arising from factors such as apple variety, cultivation practices, and processing methods [74]. To ensure reliable and reproducible results, it is essential to use standardized extracts with consistent polyphenol content. This approach is key to maintaining the quality and effectiveness of research, products, and applications related to APs. The safety and toxicity of APs are generally considered of utmost importance, especially when considering long-term use and potential high doses [74,75]. A thorough evaluation must be conducted to fully understand the long-term safety and potential toxicity of APs. This is essential in ensuring the well-being of individuals who may be prescribed these medications.

5.2. Future directions

Rigorous clinical trials are essential to establish the efficacy and safety of APs in human subjects [76]. These trials should be designed to investigate the

potential of APs in preventing and treating cancer and diabetes and their role in promoting healthy aging [77]. These trials must adhere to rigorous scientific standards to provide reliable evidence of the benefits and risks of using APs in clinical settings. We can only truly understand the potential impact of APs on human health and disease through robust clinical trials. Further investigation into the mechanistic pathways by which APs exert their anti-cancer and anti-aging effects is essential for a comprehensive understanding of their therapeutic potential [78]. By elucidating these precise molecular mechanisms, we can pave the way for developing targeted therapies and combination treatments [79]. This deeper knowledge will ultimately enhance our ability to harness the full potential of APs in the fight against cancer and aging-related conditions [80]. In the field of medicine, the potential synergistic effects of combining antipsychotic medications with other natural compounds or conventional therapies have garnered significant interest. This exploration of combination therapies holds promise in enhancing the therapeutic efficacy of antipsychotic medications while potentially reducing their associated side effects. By delving into these combinations, researchers and healthcare professionals aim to optimize treatment outcomes for individuals with mental health conditions.

6. Conclusion

APs, potent antioxidant, anti-inflammatory, anti-cancer, and anti-aging properties, hold immense promise as therapeutic agents for promoting human health (Fig. 3). Their ability to target multiple hallmarks of cancer and aging, including oxidative stress, inflammation, cell proliferation, apoptosis, angiogenesis, DNA damage, autophagy, metabolic dysfunction, and cellular senescence, underscores their potential in preventing and treating age-related diseases. Future research should focus on overcoming the challenges of bioavailability and standardization, conducting rigorous clinical trials, and exploring synergistic combinations to harness these remarkable compounds' therapeutic potential fully. As we unravel the intricate mechanisms underlying their health benefits, APs may be a powerful ally in the quest for longevity and disease prevention.

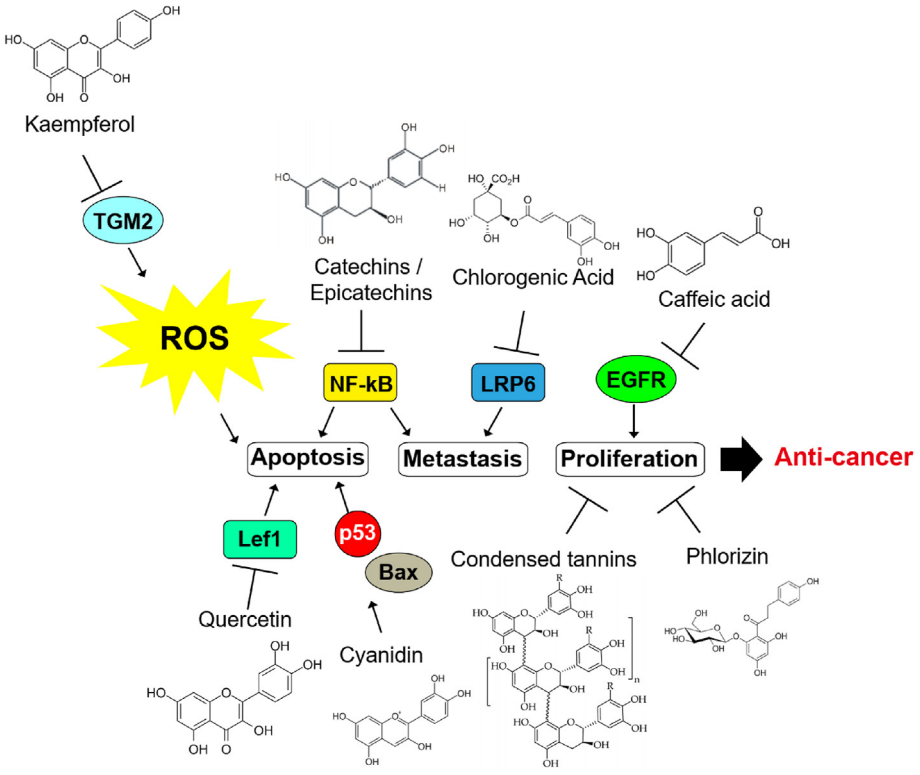

Fig. 3. In summary, the potential clinical applications of APs are promising, particularly in the fields of cancer prevention, anti-aging, and overall human health. However, several challenges need to be addressed for their effective utilization in clinical settings. Enhancing the bioavailability of APs, ensuring their safety and toxicity profiles, and conducting rigorous clinical trials are essential steps in fully realizing their therapeutic benefits. Furthermore, understanding the mechanistic pathways through which APs exert their effects and exploring potential synergistic combinations with other therapies are crucial for optimizing treatment outcomes. As research continues to unravel the intricate mechanisms underlying the health benefits of APs, they hold significant promise in the quest for longevity and disease prevention.

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