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Targeting pro-senescence mitogen activated protein kinase (Mapk) enzymes with bioactive natural compounds

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ABSTRACT

Aging is a multifactorial universal process characterized by a gradual decrease in physiological and biochemical functions. Given that life expectancy is on the rise, a better understanding of molecular mechanisms of the aging process is necessary in order to develop anti-aging interventions. Uncontrolled cellular senescence promotes persistent inflammation and accelerates the aging process by decreasing tissue renewal, repair and regeneration. Senescence of immune cells, immunesenescence, is another hallmark of aging. Targeting pro-senescent enzymes increases survival and therefore the lifespan. Although the upregulation of Mitogen Activated Protein Kinases (MAPK) enzymes in aging is still controversial, increasing evidence shows that dysregulation of those enzymes are associated with biological processes that contribute to aging such as irreversible senescence. In this manuscript components of the MAPK pathway will be summarized, including extracellular signal-regulated kinase 1 and 2 (ERK1/2), c-Jun N-terminal kinase (JNK) and p38, as well as natural flavonoids, phenolic and diterpenoids with anti-senescence activity that shows positive effects on longevity and MAPK inhibition. Although more studies using additional aging models are needed, we suggest that these selected natural bioactive compounds that regulate MAPK enzymes and reduce senescent cells can be potentially used to improve longevity and prevent/treat age-related diseases.

1. Introduction

Aging is a multifactorial universal process that occurs at molecular, cellular and tissue levels and is characterized by a gradual decrease in physiological and biochemical functions. Recent scientific discoveries have been fundamental in understanding the molecular mechanism(s) of aging and longevity. This includes a series of mechanisms such as deregulated autophagy, mitochondrial dysfunction, shortening of telomeres, oxidative stress, systemic inflammation and metabolic dysfunction that lead the cells to a senescent state in which the cell cycle is arrested (López-Otín et al., 2013). Under normal conditions, senescent cells release a series of proinflammatory factors, such as cytokines acting as a stimulus to be removed by the immune system, but persistent cellular senescence is a form of cell aging that is able to encourage the aging process by decreasing tissue renewal, repair and regeneration (López-Otín et al., 2013). In fact, progressive increase of senescent cells with age has been reported to be a hallmark of aging mammalian tissues. Senescent cells secrete growth factors, proteases, and inflammatory cytokines, known as the senescence-associated secretory phenotype (SASP). An excellent review by McHugh and Gil summarized the cellular and molecular links between cellular senescence, aging and age-related diseases as well as some therapeutic approaches (McHugh and Gil, 2018). However, with age there is a decrease in the regenerative potential due to the reduction of stem cells in the tissues (López-Otín et al., 2013). One of the factors contributing to senescence is the dysregulation of autophagy, which leads to an accumulation of cellular waste within the cell, since autophagy is a process of lysosomal degradation that cleans the cell of protein aggregates, toxic substances, aged organelles, etc. Autophagy is mainly downregulated by the mammalian target of the rapamycin (mTOR) complex that is activated under nutrient-rich conditions, but in nutrient-poor conditions, mTOR is directly inhibited by AMP-activated protein kinase (AMPK) and therefore activates the autophagy (Russell et al., 2014). During aging, the upregulation of mTOR complex and downregulation of AMPK leads

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Abbreviations

5-FU 5-fluorouracil
ACR Acrylamide
AICAR 5-Aminoimidazole-4-carboxamide ribonucleotide
AMP/ATP Adenosine monophosphate/adenosine triphosphate
AMPK AMP-activated protein kinase
CR Calorie restriction
CRP C reactive protein
CsA Cyclosporine A
CVD Cardiovascular diseases
ERK1/2 Extracellular signal-regulated kinase 1 and 2
FOXO Forkhead box O transcription factors
HDAC Histone deacetylases
hnRNP A1 Heterogeneous nuclear ribonucleoprotein A1
IF Intermittent fasting
IGF-1 Insulin/growth factor-1
JNK c-Jun N-terminal kinase
LPLI Low-power laser irradiation
MAPK Mitogen Activated Protein Kinases
MAPKKKs MAPK kinase kinases
MAPKKs MAPK kinases
MSCs Mesenchymal stem cells
mTOR mammalian target of the rapamycin
NAD$^+$/NADH Nicotinamide adenine dinucleotide/reduced nicotinamide adenine dinucleotide
NF-ƙβ Nuclear factor Kappa B
PGC-1α/PGC-1β Proliferator activated receptor γ coactivators α, β
PPARβ/δ Peroxisome proliferator-activated receptor beta/delta
ROS Reactive oxygen species
SASP Senescence-associated secretory phenotype
SA-βgal Senescence-associated beta-galactosidase
SCs Satellite cells
SOCS3 Suppressor of cytokine signaling 3
SOD Superoxide dismutase
TERT Telomerase reserve transcriptase
TGF-β1 Transforming growth factor
TNF-α Tumor necrosis factor-α
WS Werner's syndrome

to a deregulated autophagy (Fig. 1).

In somatic cells, after each cell division, part of the telomere is lost, inducing telomere shortening, which is another hallmark of molecular aging (López-Otín et al., 2013). This process occurs in a limited number of cell divisions until the critical telomere size is reached, then the cells become senescent, losing the function of telomeres in the maintenance of the genome and promotion of stability in the processes of replication. In some cellular lineages, such as stem cell, telomere can be restored by the enzyme telomerase reverse transcriptase (TERT). Several studies have reported that inducing TERT activity in somatic cells reverses several characteristics of aging, such a senescent (Bär and Blasco, 2016).

In 1956, Harman proposed a free radical theory of aging that suggested the role of reactive oxygen species (ROS) and oxidative stress in the process of aging are factors that aggravate the damage in cellular biomolecules (Harman, 1956). However, recent evidence shows that ROS have a double effect. They act, initially, as an activator of the homeostatic compensatory response, which increases with age and activates several antioxidant mechanisms in order to maintain survival and, from a certain level, makes injuries related to aging worse (Hekimi et al., 2016), suggesting that ROS effects are dependent on where they are present and on their concentration. Another mechanism associated with aging is the increase of proinflammatory agents, such as tumor necrosis factor-α (TNF-α) or interleukines (IL-1 β, IL-6), which is known as “inflammaging”. Overexpression of ROS is essential for activating transcription factors, such as the activator of protein-1 (AP-1) and the nuclear factor Kappa B (NF-kB) that regulates the expression of these proinflammatory agents and contributes to the aging process (Fougère et al., 2016). In addition, mitochondrial dysfunction is associated with chronic oxidative stress in aging. The proliferator activated receptor γ coactivators α, β (PGC-1α and PGC-1β) is one of the main regulators of mitochondria. It responds to changes in nutrient status, such as the ratio of nicotinamide adenine dinucleotide/reduced nicotinamide adenine dinucleotide (NAD$^+$/NADH) and adenosine monophosphate/adenosine triphosphate (AMP/ATP), which are regulated through SIRT1 and AMPK, respectively. In aging, NAD$^+$ levels decrease, which leads to a downregulation of SIRT1 activity inducing changes in several genes, including the decrease of PGC-1α/β, which leads to a decline in mitochondrial biogenesis (Fang et al., 2016). On the other hand, AMPK, which is activated by high energy stress, works in the same direction as SIRT1 and contributes to longevity, along with senescence proliferative arrested by upregulating the activity of p53 and retinoblastoma protein (Wiley and Campisi, 2016).

In general, aging is characterized by a deficiency of cellular energy fundamentally due to autophagy and mitochondrial dysfunction. Several factors are involved in this process. One of the most characteristic being the insulin/growth factor-1 (IGF-1), which in a high level is associated with aging but improves healthspam and longevity when present at low levels (Martins et al., 2016). The IGF-1 pathway regulates Forkhead box O (FOXO) transcription factor family, which have been shown to prolong the lifespan by activating genes that promote resistance to oxidative stress, DNA repair or cellular detoxification. Upon PI3K/AKT activation by IGF-1, the kinase AKT phosphorylate FOXO, promotes its cytoplasm localization and inhibits the expression of FOXO-dependent genes, which lead to a reduction of beneficial effects of FOXO in the lifespan (Martins et al., 2016).

These above mechanisms are all inter-connected; however, control of their processes remains unclear. Therefore, more research is necessary, specifically aimed at the molecular processes of organism aging that improves human health and the lifespan. Over the years, several anti-aging interventions such as caloric restriction, telomerase and autophagy activation, as well as senolitic, epigenetic and stem cell modulators, have been studied. One of the most promising approaches to a successful anti-aging strategy includes the activation of enzymes such as AMPK, SIRT1, ATG13 as potential longevity factors. Another approach to enhance survival and the lifespan can be focused on the

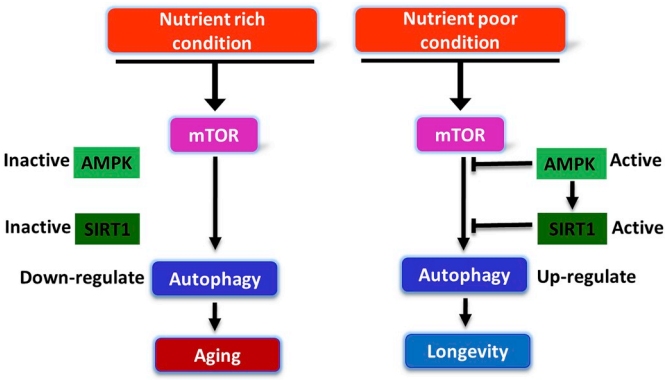

Fig. 1. Regulation of Autophagy by mTOR and AMPK in Response to Nutrient. Under nutrient-rich conditions mTOR downregulate the autophagy and contribute to aging process, but in nutrient-poor conditions, mTOR is inhibited by AMPK and SIRT1 resulting in the upregulation of autophagy and promoting longevity.

inhibitions of pro-aging enzymes such as PI3K/Akt, mTOR, P70S6k or Mitogen Activated Protein Kinases (MAPK). In this sense, the goal of this review is to analyze several bioactive natural compounds targeting the specific pro-aging enzymes MAPK, which play a key role in regulating important events such as oxidative stress, inflammation, proliferation, differentiation, apoptosis and stress response all of which contribute to aging.

2. Mitogen activated protein kinase (Mapk) and aging

Protein phosphorylation mediated by kinase enzymes has a key role in signaling transduction pathways. Previously we summarized the relevance of the phosphorylation process mediated by kinase enzymes, which are responsible for transferring the phosphoryl group from one nucleotide to protein targets, as well as the phosphoproteomic approaches for elucidating their molecular mechanisms in diseases, and the potential use of kinase inhibitors for anti-aging intervention (Cano et al., 2017). Mitogen activated protein kinase (MAPK) enzymes are usually regulated by phosphorylation and typically constituted by three kinases enzymes: MAPK kinase kinases (MAPKKKs), MAPK kinases (MAPKKs), and MAPKs. MAPKs pathway is an evolutionarily conserved signaling pathway associated with essential biological processes including proliferation, differentiation, apoptosis and stress response. MAPK can be broadly classified into two groups: **i)** classical or conventional (e.g. extracellular signal-regulated kinase 1, 2 and 5, p38s and c-Jun N-terminal kinase), which are principally phosphorylated on the conserved Thr–Xaa–Tyr motif within the activation loop by the MAPKK family members MKK family, and **ii)** atypical (e.g. Nemo Like Kinase and extracellular signal-regulated kinase 3, 4 and 7) which are phosphorylated and activated on different Thr–Xaa–Tyr motif, where a glycine or glutamic acid residue replaces the tyrosine. In this review we focus on classical MAPK pathways because the regulation and physiological functions of atypical MAPK remain to be fully elucidated. In this context, Coulombe and Meloche (2007) summarized the structure, regulation, mechanisms of activation, substrates and physiological function of the atypical MAPK family (Coulombe and Meloche, 2007).

Along with that, in an excellent manuscript Plotnikov and colleagues summarized the composition, function and nuclear activities of the classical MAPK pathway (Plotnikov et al., 2011). In mammalian organisms the main components of the MAPK pathway are extracellular signal-regulated kinase 1 and 2 (ERK1/2), c-Jun N-terminal kinase (JNK), p38, and ERK5 (Fig. 2). Mitotic stimuli can induce the activation of ERKs pathways, while cellular/environmental stress is the most important stimuli able to activate JNK and p38 pathways (Plotnikov et al., 2011).

Although the up-regulation of MAPK enzymes in aging is still controversial, increasing evidence shows that dysregulation of those enzymes are linked to the initiation and progression of the inflammation process. Chronic low grade inflammation is linked to age-associated diseases such as neurodegenerative diseases, cancer, cardiovascular diseases (CVD) and diabetes (Yeung et al., 2018). In this context, it has been postulated that the aging process can be a consequence of the imbalance between high activity of inflammatory pathways (inflammaging) and low activity of anti-inflammatory pathways (anti-inflammaging) (Franceschi et al., 2007). Recently, the inflammation theory of aging was summarized and contextualized by Monti et al. (2017). The authors suggest that an uncontrolled modulation of pro-inflammatory pathways and an unsuccessful anti-inflammatory response contribute to chronic age-related pathologies. On the other hand, healthy aging and longevity are promoted by an effective anti-inflammatory response. In fact, in patients with extreme longevity and successful aging (centenarian), their increased levels of pro-inflammatory molecules including interleukin (IL6, IL18 and IL15), C reactive protein (CRP), serum-amyloid A, fibrinogen, Von Willebrand factor, resistin and leukotrienes, are effectively compensated by increasing levels of anti-inflammatory molecules such as adiponectin, transforming growth factor (TGF)-β1, interleukin 1 receptor antagonist (IL-1RA), a peptide that blocks the inflammatory effect of IL-1 by binding to the IL-1 receptor, cortisol, and finally anti-inflammatory arachidonic acid compounds. Moreover, the authors showed that approaches designed to decrease and control inflammaging represent a powerful tool to modulate chronic age-related diseases while extending the healthspan of a population (Monti et al., 2017).

Considering that MAPK enzymes are essential modulators of general inflammation, and that this increased inflammation is linked to age, the expectation being that MAPK enzymes are upregulated with aging. Moreover, it could also be possible that physiological levels of MAPK enzymes contribute to the delay of irreversible senescence while promoting longevity. However, an excessive activation of MAPK enzymes and their deficient response capacity, which might progress with aging, could lead to promotion of both irreversible cellular senescence and an accelerated aging process. This is a relevant issue because normal activation of MAPK is necessary to accurate stress response and cell survival, but their uncontrolled activation can promote inflammation and inflammatory-related pathologies, which contribute to an acceleration of the aging process. In general, upregulation of MAPK promotes irreversible senescence in T cells; however, different MAPK enzymes stimulate specific senescence markers. For example, pharmacological or

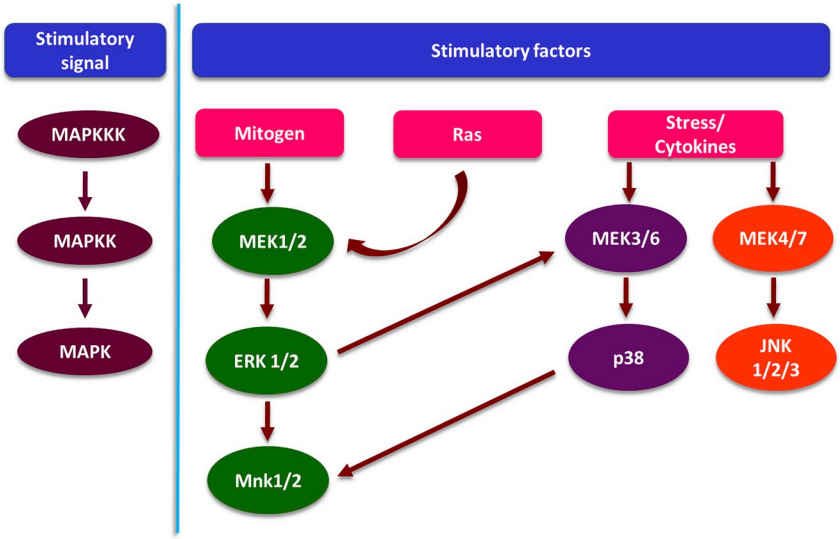

Fig. 2. MAPK Signaling Pathway. Mitogen activated protein kinase (**MAPK**) enzymes are usually regulated by phosphorylation and typically constituted by three kinases enzymes: MAPK kinase kinases (**MAPKKKs**), MAPK kinases (**MAPKKs**), and MAPKs. In mammalian organisms the main components of the MAPK pathway are extracellular signal-regulated kinase 1 and 2 (**ERK1/2**), c-Jun N-terminal kinase (**JNK**), and p38. Mitotic stimuli activate ERKs pathways, while cellular/environmental stress stimuli activate JNK and p38 pathways.

genetic specific inhibition of p38, but not of JNK or ERK, enhance telomerase activity, inhibition of ERK, but not of p38 or JNK, reduce DNA damage foci, and inhibition of JNK, but not p38 or ERK, promote the re-expression of the key T cell receptor signalosome component Lck (Lanna et al., 2017).

2.1. p38 MAPK pathway

The p38 MAPK pathway, which is associated with the two major contributors of aging (oxidative stress and inflammation), is upregulated in aging. In fact, Li and colleagues reported an increased regulation and activation of p38 MAPK pathway in lung and brain homogenates from a 20-month-old male rat compared to a young 2-month-old male C57BL/6 J. In those mice, authors also found a concomitant increase of pro-inflammatory cytokines TNF-α, IL-1β and IL-6, and a decrease of antioxidant machinery (analyzed as superoxide dismutase (SOD)) as well as glutathione (GSH) levels (Li et al., 2011). Klotho is an aging-suppressor gene because overexpression of Klotho extends the lifespan whereas its depletion leads to premature aging and death. In this context, Hsieh and colleagues suggest that reduction of p38 MAPK activity increased stress resistance and promoted longevity. The authors found that in mouse models of aging, Klotho attenuated phosphorylation of the p38 MAPK catalytic site amino acids (Thr180/Tyr182) in the Klotho overexpressing mouse liver and phosphorylation of the catalytic site amino acids (Thr180/Tyr182) was increased in Klotho-ablation livers (Hsieh et al., 2010). The lamins family of proteins (A/C/B) are essential components of the inner nuclear membrane; alteration of the nuclear shape is generally associated with senescence and the aging process. Using primary human fibroblasts, it was reported that upregulation of lamin B1 promoted senescence because of an increase in the percentage of SA-β-gal-positive cells, a decrease in cell proliferation and an induced alteration in chromatin structure. The authors also found that p38 MAPK activation contributes to oxidative stress-induced senescence through upregulation of lamin B1 protein (Barascu et al., 2012). Werner's syndrome (WS) is a severe premature aging pathology associated with accelerated cell senescence. Davis and colleagues reported that p38 MAPK has an important role in the reduction of accelerated cell senescence because p38 MAPK inhibitors (SB203580, BIRB 796, VX-745 and UR13756) increased growth rates, replicate capacity and reduced the stressed cellular morphology, a characteristic of senesced cells (Davis et al., 2016).

Several reports suggest that p38 can regulate cellular senescence and SASP in different cell types. For example, in normal human fibroblast when p38 is activated results show the repression of hTERT gene and induction of cellular senescence (Harada et al., 2014). Moreover, p38 is activated in response to oncogenic *RAS*-induced premature senescence. The authors suggest that p38δ may participate in the activation of DNA damage pathways in response to oncogenic *RAS* because p38δ depletion decreased the *RAS*-induced activating phosphorylation of Chk1 and Chk2, two DNA damage checkpoint kinases (Kwong et al., 2013). In response to oxidative stress, p38 contributes to the formation of the senescent phenotype through a mechanism involving inhibition of acetyl-CoA carboxylase 1, the enzyme that catalyzes the rate-limiting step in lipid synthesis (Marmisolle et al., 2017). The activity of p38 was enhanced in aged beige progenitors and treatment with p38 inhibitor (SB203580) reduced the expression of senescence-activating genes and increased senescence inhibitory genes. SB203580 also reduced the number of senescence-associated beta-galactosidase (SA-βgal) positive cells suggesting a rejuvenated cell (Berry et al., 2017).

UVB light is a known inducer of premature senescent keratinocytes. In this context, Kim and colleagues reported that in human keratinocytes, the ability of adiponectin to reduce senescence associated markers (SA-β-gal activity, $p16^{INK4\alpha}$ and phosphorylated H2AX protein expression) is linked to suppression of p38 and JNK/SAPK signaling (Kim et al., 2016). Senescent chondrocytes accumulate with age and pathogenesis of osteoarthritis. Kang and colleagues associated the effect of Cyclosporine A (CsA) and FK506 (also known as tacrolimus) as able to reduce the induction of senescence of articular chondrocytes through downregulation of p38 because both, CsA and FK506 inhibited p38 phosphorylation (Kang et al., 2016).

In addition to p38 inhibitor SB203580, which has been associated with the reduction of senescence, the two next-generation p38 inhibitors (UR-13756 and BIRB 796) with better selectivity and specificity compared to SB203580, were also able to diminish senescence-associated IL-6 secretion in human fibroblast (Alimbetov et al., 2016). Excessive exposure of ROS such as hydrogen peroxide (H_2O_2) could induce mesenchymal stem cells (MSCs) into premature senescence. Melatonin could be a potential candidate to protect MSCs from H_2O_2-induced premature senescence because treatment with melatonin increased cell proliferation and proportion in the S phase, enhanced osteogenic differentiation of senescent cells, decreased SA-β-gal-positive cells and increased expression of *SIRT1* while reducing expression of $p16^{INK4\alpha}$ and p-p38 (Zhou et al., 2015). Moreover, in response to direct DNA damage or oncogenic RAS, p38 activation promote SASP in normal human fibroblasts through NF-κβ transcriptional activity, which was required for the expression of most SASP factors; p38 MAPK activation during senescence was blocked by SB203580 (Freund et al., 2011).

T cell senescence contributes to immune function decline with age. Interestingly, p38 activation mediated by AMPK is associated with the senescence of different cell types including T cells, fibroblasts and cardiomyocytes. For example, senescence in human $CD8^+$ T cells are mediated by p38 signaling. In fact, inhibition of p38 with specific small-molecule inhibitor BIRB 796, improved telomerase activity, mitochondrial function, increased autophagy, releasing metabolic precursors and allowed the cell to increase its proliferative capacity (Henson et al., 2014). Heterogeneous nuclear ribonucleoprotein A1 (hnRNP A1) is an RNA binding protein that plays an important role in the biogenesis of mRNA, its downregulation and its cytoplasmic accumulation contribute to a partial senescence-like morphology Inhibition of p38 activity upregulated hnRNP A1 protein expression in young rats and in G_0-arrested cells, as well as inhibited cytoplasmic accumulation of hnRNP A1 in senescent cells (Shimada et al., 2009). Upregulation of p38 is also associated with age-related pathologies. For example, (**i**) in modulation of endothelial senescence and cardiovascular aging, where high activity of p38 was found in senescent endothelial cells (Wu et al., 2015); (**ii**) sarcopenia, skeletal muscle aging can lead to sarcopenia, and poor regenerative capacities of sarcopenic muscle are associated with aged satellite cells (SCs) dysfunction. It has been found that loss of self-renewal in aged SCs was linked to upregulation of p38 and partial inhibition of p38 with SB203580 improved aged SCs self-renewal (Bernet et al., 2014).

While a growing number of reports clarify that upregulation of p38 promotes irreversible or premature senescence and aging, and inhibition of p38 could be a potential therapeutic approach for control of aging and treatment of age-related pathologies, other reports show that p38 activity contributes to enhanced longevity in non-mammalian species. In fact, in *Drosophila*, upregulation of p38K in muscle tissue extends the life-span through a mechanism involving MnSOD; however, downregulation of p38K causes early lethality and contributes to age-related motor dysfunction and stress sensitivity (Vrailas-Mortimer et al., 2011). Similarly, downregulation of the conserved PMK-1 p38 MAPK, which mediates the expression of secreted immune response genes, was linked to *C. elegans* aging because a progressive reduction in the activated PMK-1 p38 MAPK was found throughout adulthood; intact immune function stimulates longevity (Youngman et al., 2011).

2.2. Jun amino-terminal kinases (JNK) MAPK pathway

Another important MAPK enzyme with a key role in oxidative stress, inflammation and that can be upregulated in aging is JNK. In fact, JNK activity increased with aging in intestinal cells (Buzzi et al., 2007).

Moreover, activity of JNKs in old rat brains increased when compared to that from young rats (Zhou et al., 2009). D-galactose has been reported to promote senescence, oxidative stress, inflammation and apoptosis. In hippocampus and cortex, D-galactose increased the expression and activation of JNK, while DL0410 was able to decrease the phosphorylation of JNK and improved cognitive defects produced by aging using a D-galactose-induced aging model (Lian et al., 2017).

Another molecule able to stimulate senescence is 5-fluorouracil (5FU). Recently it has been reported that 5FU produces senescence of endothelial cells through a mechanism involving increased p38 and JNK activity as well as reduction of eNOS and SIRT1 levels (Altieri et al., 2017). Activating transcription factor 3 (ATF3) is an important gene associated with genotoxic stress response. The senescence induced in macrophages by acrylamide (ACR), a genotoxic carcinogen, is mediated by increased activation of p38 and JNK enzymes, which stimulate the ATF3/p53/p21 pathway leading to cellular telomerase-independent senescence (K.-H. C.D. Kim et al., 2015). In hippocampus, the age-dependent increased expression and activation of two pro-inflammatory modulators, IL-1β and JNK, were associated with decreased activation of survival pathways (Akt/p70S6K and MEK/ERK). The authors also reported that treatment with sodium ferulate, an anti-oxidant and anti-inflammatory compound, was able to prevent age-related changes in rats (Jin et al., 2008).

The decrease of muscle mass with age, also called sarcopenia, and reduced testosterone levels are both a common hallmark of aging. In aged muscles, oxidative stress is increased and the expression and activation of p21 and JNK are upregulated. The positive effect of testosterone on muscle growth in those old mice was mediated by inhibition of myostatin, p21 expression, JNK activity, activation of Akt and Notch signaling, and re-establishment of G6PDH levels (Kovacheva et al., 2010). In kidney isolated from young, middle-aged and old rats, a significant age-related increase of oxidative stress, p38, JNK and ERK enzymes were found. Using calorie restriction (CR) and intermittent fasting (IF) as anti-aging and anti-oxidative approaches, it was found that CR significantly decreases both the age-related activation of MAPK enzymes and the age-related oxidative stress. Moreover, IF was able to decrease JNK activity in the cortex of senescence-accelerated prone-8 mice, which have a shorter lifespan (Tajes et al., 2010). Another anti-aging approach is exercise. In fact, in rat skeletal muscle the increase of JNK activation with aging was reduced by acute exercise. Moreover, other age-related changes such as reduction in glucose disappearance rate and SIRT1 expression, increase in the expression of protein tyrosine phosphatase 1B, phosphorylation of IRS-1 and IkBα degradation were improved by exercise (Pauli et al., 2010). Similarly, it was reported that activity of JNK is increased in skeletal muscle from older men as compared to young men (Ghosh et al., 2015).

It is accepted that JNK is activated by stress, and stress contributes to aging and age-related neurodegeneration. In hippocampus, which is particularly vulnerable to stress and aging, the activity of JNK was found to be strong, but not -significantly so, and it increased in old mice as compared to control. However, the JNK activity was significantly increased in the chronic mild stress aged group compared to control and aged mice, suggesting that pro-aging effects of stress could be mediated, at least in part, by JNK (Solas et al., 2013). Another structure vulnerable to stress and aging is the retina. In fact, Zhao and colleagues found a significant increase of JNK and p38 activity in aged retina tissue, showing bigger stress stimuli in aged retina rats (Zhao et al., 2014). Aging is a risk factor of increasing susceptibility to arrhythmias because in the heart the upregulation of stress pathways gradually increases during aging. Recently, it has been reported that in the right atrial muscle of guinea pigs, the age-dependent increase of JNK activity can lead to an increasing risk of atrial arrhythmias with advancing age, this risk being associated with a decrease of connexin-43 protein expression, essential for preserving electrical atrial conduction (Jones and Lancaster, 2015).

Similar to p38, several studies show that JNK has an essential role in promoting cellular senescence and in contributing to an accelerated aging process. However, it has also been reported that the upregulation of JNK activity is important in avoiding premature senescence while promoting longevity. For example, depletion of JNK activity promotes premature senescence in breast carcinoma, lung carcinoma cancer cell line and embryonic fibroblasts. In fact, pharmacologic (SP600125) and genetic (siRNA) inhibition of JNK activity promotes premature senescence, downregulation of Bcl2, increases ROS mitochondrial production and DNA-damage response. The authors also found that basal JNK activity is essential in preventing premature senescence and maintaining cell proliferation (Lee et al., 2010). Finally, in *C. elegans* and in *Drosophila*, JNK modulates stress resistance and promotes longevity (Biteau et al., 2011; Oh et al., 2005).

2.3. Extracellular signal-regulated kinase (ERK) MAPK pathway

An additional MAPK enzyme with a key role in oxidative stress, inflammation which can be upregulated in aging is ERK. In fact, it has been reported that ERK is able to inhibit the activation of AMPK, which is essential in controling the aging process and to extend both healthspan and lifespan through modulation of FOXO, mTOR and SIRT1 signaling pathways (Salminen et al., 2016). In different cell types and in response to specific stimulus, ERK activity can promote senescence *in vitro* and *in vivo*. Recently, Cagnoland Chambard showed that irregular activation of the Ras /Raf /ERK pathway can stimulate oncogenic transformation of immortalized cells as well as senescence of primary cells. The mechanisms of ERK-induced senescence summarized by the authors include upregulation of β-galactosidase activity and stimulation of classical senescence-associated genes, such as $p16^{INK4\alpha}$, p53, p21 and p14-p19/ARF, senescence-associated heterochromatic foci and DNA damage foci (Cagnol and Chambard, 2010). Moreover, different studies have reported that tumor-suppressive action of several natural anti-oxidative drugs such as curcumin, sulforaphane and baicalin are mediated by ERK-induced senescence. This is because increased activation of ERK and senescence markers (e.g. increase of SA-βgal positive cells and $p16^{INK4\alpha}$ protein levels, as well as the decline of phosphorylation levels of pRb) were found in colon cancer cells treated with these compounds *(See more detail in* Table 1*)*. Furthermore, in rat embryo fibroblasts an increased activation of ERK was found when senescence was induced with sodium butyrate (HDAC inhibitor) (Wang et al., 2018). It is also known that activation of MAPK signaling is important in photo-aging. Upregulation of MAPK enzymes including ERK, JNK and p38 phosphorylation levels during UVB-induced fibroblast senescence (Lei et al., 2017). Age-related increase of ERK activity in the rat heart was associated with decreased STAT3 activation and SOCS3 levels, while alternate-day fasting treatment was able to decrease ERK activity and increase STAT3 activation and SOCS3 levels (Castello et al., 2011). Similarly, other authors found an increase of ERK activity in rat aged heart lysates and heart sections (Cieslik et al., 2013). Moreover, Sieslik and colleagues reported that when mesenchymal fibroblasts, derived from aged mice hearts, were treated with AICAR, an AMPK activator, the activation of ERK decreased by 30% (Cieslik et al., 2017).

Cranberry, a natural product rich in bioactive phytochemicals, can promote healthy aging. The anti-aging effect of cranberry is mediated by stress response MAPK signaling. In fact, a reduction of the accumulation of oxidative damage and downregulation of ERK activity were found in *Drosophila* after supplementation with cranberry (Sun et al., 2014). Inhibition of ERK extends the lifespan because both genetic (using RNAi knockdown of *rl, Drosophila* ortholog of Erk*)* and pharmacology (using trametinib, potent and highly specific inhibitor of the Mek kinase, preventing activation of Erk by Ras) inhibition of ERK activation was able to increase the lifespan in *Drosophila* (Slack et al., 2015). PPARβ/δ is a nuclear receptor that can inhibit skin tumorigenesis. In keratinocytes and skin tumors, PPARβ/δ encourages HRAS-induced senescence through upregulation of RAF/MEK/ERK pathway and

Table 1
Bioactive natural compounds that increase longevity and inhibit MAPK enzymes.

IUPAC/Chemical Name	Experimental model, Dose and Effect on longevity	Experimental model, Dose and Effect on MAPK (ERK, p38, JNK)	Pharmacological effect
Acacetin (5,7-dihydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one), is a naturally occurring flavonoid. This natural flavonoid is present in several plants such as thistle, safflower seed or acacia.	Caenorhabditis elegans 5 μM: ↑17.24% lifespan 25 μM: ↑27.31% lifespan 50 μM: ↑11.25% lifespan (Asthana et al., 2016a)	6-OHDA-induced cell toxicities 5-10 μM: ↓ p-p38 10 μM: ↓ p-JNK (S. M. Kim et al., 2017)	↑ Neuroprotecction, ↓ Apoptosis, ↓ Mitochondrial dysfunction.
	Caenorhabditis elegans 5 μM: ↑10.11% lifespan 25 μM: ↑39.00% lifespan 50 μM: ↑16.95% lifespan (Asthana et al., 2016b)	Fibroblast-like synoviocytes 5-10 μM: ↓ p-p38 10 μM: ↓ p-JNK (Chen et al., 2015)	↓ Inflammation
		LPS-activated BV-2 cells 10 μM: ↓ p-p38 (Ha et al., 2012)	↓ Neuroinflammation
		Human breast cancer MCF-7 cells 100 μM: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (Shim et al., 2007)	↓ Proliferation, ↑ Apoptosis
		Human umbilical vein endothelial cells 30 μM: ↓ p-p38 (Tanigawa et al., 2013)	↓ Inflammation, ↓ Proliferation
		GalN/LPS-induced fulminant hepatic failure in mice Acacetin 100 mg/ kg body weight: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (Cho et al., 2014)	↓ Inflammation, ↑ Autophagy
		Myocardial infarction in mice 10 mg/kg body weight/day: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (Chang et al., 2017	↓ Inflammation, ↓ Apoptosis
Baicalein (5,6,7-trihydroxy-2-phenylchromen-4-one), is a flavonoid derived from *Scutellaria baicalensis* (Chinese medicinal herb Huang-chin)	Caenorhabditis elegans 100 μM: ↑16 – 30 % lifespan (Havermann et al., 2016)	(LPS)-stimulated macrophages (RAW264.7 cells) 10 - 25 - 50 μM: ↓ p-ERK ↓ p-p38, ↓ p-JNK (Luo et al., 2017)	↓ Inflammation, ↓ Apoptosis
	Caenorhabditis elegans 100 μM: ↑24 % lifespan (Havermann et al., 2013)	Lysophosphatidylcholine -induced cytotoxicity in rat H9c2 embryonic cardiomyocytes 1 - 5 - 10 μM: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (H.-M. Chen et al., 2014)	↓ Apoptosis
		Monocrotaline-induced pulmonary arterial hypertension in Sprage-Dawley rats (Lung tissue and Right ventricular tissue) 50 and 100 mg/kg body weight/day: ↓ p-ERK, ↓ p-p38, ↓ p-JNK. (Shi et al., 2018)	↓ Inflammation, ↓ Apoptosis
		Abdominal aortic aneurysms in Apoe$^{-/-}$ mice infused with angiotensin II 30 mg/kg body weight/day: ↓ p-p38, ↓ p-JNK (Wang et al., 2016)	↓ Inflammation, ↓ ROS
		Cancer-Induced Bone Pain in Sprague-Dawley rats Intrathecal 100 μg: ↓ p-p38, ↓ p-JNK (Hu et al., 2015)	↑ Neuroprotecction, ↓ Inflammation
		LPS-induced mastitis in BALB/c mice (mammary tissue) 5 – 10 - 20 mg/kg body weight/day: ↓ p-ERK, ↓p-p38, ↓ p-JNK (He et al., 2015)	↓ Inflammation
		Unilateral ureteral obstruction-induced renal fibrosis in C57/BL6 mice (kidneys) 50 - 100 mg/kg body weight/day: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (Wang et al., 2015)	↓ Inflammation
		Lung Injury Induced by Myocardial Ischemia and Reperfusion in Sprague-Dawley rats (Right lung) 3 - 10 - 30 mg/kg body weight/day: ↓ p-p38, ↓ p-JNK (Lai et al., 2016)	↓Kidney injury, ↓ myocardial ischemia, ↓ reperfusion.

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Table 1 (*continued*)

IUPAC/Chemical Name	Experimental model, Dose and Effect on longevity	Experimental model, Dose and Effect on MAPK (ERK, p38, JNK)	Pharmacological effect
Chlorogenic acid (1S,3R,4R,5R)-3-[(E)-3-(3,4-dihydroxyphenyl) prop-2-enoyl]oxy-1,4,5-trihydroxycyclohexane-1-carboxylic acid, is the major polyphenolic compound in coffee, isolated from the leaves and fruits of dicotyledonous plants.	Caenorhabditis elegans 50 μM: ↑27.1 % lifespan (S.-Q. Zheng et al., 2016)	Liver tissue from male ICR mice with polymicrobial sepsis induced 20 mg/kg body weight: ↓ p-p38, ↓ p-JNK (Lee et al., 2013)	↓ Inflammation, ↓ Apoptosis
		Sprague-Dawley rats with hepatic sinusoidal obstruction syndrome 20 mg/kg body weight: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (Z. Zheng et al., 2016)	↓ Inflammation, ↑Antioxidants
		Acetaminophen-induced liver injury in ICR mice 40 mg/kg body weight: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (Ji et al., 2013).	↓ Inflammation, ↓ Apoptosis
		Platelet derived growth factor (PDGF)-induced fibrosis in rat hepatic stellate cells (HSC-T6) 10 ng/mL: ↓ p-ERK, ↓ p-p38 (Shi et al., 2016).	↑ Antioxidants, ↓ Oxidative stress
		RANKL-mediated osteoclast differentiation in bone marrow macrophages 10, 25 and 50 μg/ml: ↓ p-p38 25 and 50 μg/ml: ↓ p-ERK 25 and 50 μg/ml: ↓ p-JNK (Kwak et al., 2013).	↓Inflammation-induced bone loss, ↓Osteoclasts differentiation
		JB6 Murine epidermal cell exposed to UVB 15 μM: ↓ p-p38, ↓ p-JNK 140 μM: ↓ p-ERK (Feng et al., 2005)	↓ Inflammation, ↓ Carcinogenesis, ↑Antioxidants
		Mouse Bone Marrow Macrophage (BMMs) treated with nuclear factor-kappa B (NF-κB) ligand. 10 – 25 – 50 μg/mL: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (Kwak et al., 2013)	↓ Inflammatory bone destruction
		H_2O_2-induced apoptosis in H9c2 cardiomyoblasts cells 12.5 - 25 μM: ↓ p-ERK, ↓ p-JNK (Yu et al., 2016).	↓ Oxidative stress, ↓ Apoptosis.
		VEGF- activated primary human retinal endothelial cells 2.5 μM: ↓ p-ERK, ↓ p-p38 (Mei et al., 2018)	↓ Retinal neoangiogenesis, ↓ Inflammation.
Epigallocatechin-3-gallate (EGCG) [(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxybenzoate, is a phenolic antioxidant found in a number of plants such as green and black tea.	Caenorhabditis elegans 100 μM: ↑20 % lifespan (Bartholome et al., 2010).	TGF-b-induced myofibroblast differentiation in prostate fibroblast cell line 40 μM: ↓ p-ERK (Gray et al., 2014).	↓ Tumor myofibroblast differentiation, ↓ Tumor cell invasion
	Caenorhabditis elegans 0.1μg/mL: ↑13.1% lifespan under heat stress and ↑ 172.9% lifespan under oxidative stress (Zhang et al., 2009).	Myocardial ischemia induced in Male Sprague–Dawley rats 10 mg/kg body weight: ↓ p-p38, ↓ p-JNK (S. J. Kim et al., 2014).	↓ Myocardial I/R injuries
	Wistar rats 25 mg /kg: ↑14.1 % lifespan (Niu et al., 2013)	Toxicity induced by nickel nanoparticles (Ni NPs) in mouse epidermal cell line 10 μM: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (In the 2.5 and 5 μg/cm2 Ni NPs treatment groups). (Gu et al., 2016)	↓ Oxidative stress, ↓ Apoptosis.
	Old C57BL/6 male mice 0.25% w/v for 37–44 wk: ↑ 30.3% (Si et al., 2019)	LPS-stimulated human acute monocytic leukemia cell line 50 μg/ml: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (T. Wang et al., 2014)	↓ Inflammation

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Table 1 (*continued*)

IUPAC/Chemical Name	Experimental model, Dose and Effect on longevity	Experimental model, Dose and Effect on MAPK (ERK, p38, JNK)	Pharmacological effect
		Human retinal endothelial cells treated with high glucose concentrations 20 - 40 μM: ↓ p-ERK, ↓ p-p38 (Zhang et al., 2016)	↓ Inflammation, ↓ Apoptosis
		LPS-induced innate signaling in bone marrow-derived macrophages isolated from ICR mice 100 μM: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (Joo et al., 2012).	↓ Inflammation
		Homocysteine -induced proliferation of vascular smooth muscle cells 20 μM: ↓ p-ERK, ↓ p-p38 (Zhan et al., 2018).	↓ Proliferation
		Pancreatic alpha TC1-6 (αTC1-6) cells exposed to H_2O_2 100 μM: ↓ p-p38, ↓ p-JNK (Cao et al., 2018).	↓ Oxidative stress, ↓ Apoptosis ↓ Dysfunction of glucagon secretion
Fisetin 2-(3,4-dihydroxyphenyl)-3,7-dihydroxychromen-4-one, is a plant polyphenol from the flavonoid group. It can be found in many plants, fruits and vegetables, such as strawberries, apples, persimmons, onions and cucumbers.	Drosophila melanogaster 100 μM: ↑23 % lifespan (Wood et al., 2004).	LPS- treated Human gingival fibroblasts 1 – 5- 10 - 15 μM: ↓ p-p38, ↓ p-JNK (Gutiérrez-Venegas et al., 2014).	↓ Inflammation
	Saccharomyces cerevisiae 10 μM: ↑55% lifespan (Howitz et al., 2003).	12-O-tetradecanoyl-phorbol-13-acetate TPA-induced cell invasion in MCF-7 human breast cancer cells 30 μM: ↓ p-ERK, ↓ p-p38 (Noh et al., 2015).	↓ Cell invasion, ↓ Inflammation
		Melanoma cells (A375 and RPMI-7951) 5 – 10 - 20 μM: ↓ p-ERK (Pal et al., 2014)	↓ Cell invasion, ↑ epithelial-mesenchymal transition,
		Human cervical adenocarcinoma (SiHa and CaSki cells) 20 – 40 μM: ↓ p-p38 (Chou et al., 2013).	↓ Cell invasion, ↓ Migration
		Primary astrocyte cultures from 1-day-old Sprague-Dawley rat brains 12.5 – 25 – 50 μM: ↓ p-ERK (N. Wang et al., 2017).	↓ Cell proliferation, ↓ Migration
		Dextran sulphate sodium-induced colitis in male Balb/C mice 5 and 10 mg/kg body weight: ↓ p-p38 (Sahu et al., 2016)	↓ Inflammation, ↑ Antioxidants, ↓ Oxidative stress
Gallic acid and its derivatives 3,4,5-trihydroxybenzoic acid, is an organic acid found in gallnuts, sumac, witch hazel, tea leaves, oak bark, and other plants.	Caenorhabditis elegans 300 μM: ↑10 % lifespan (Saul et al., 2011)	High fat diet/ streptozotocin-induced Diabetes in wistar albino rats 25 and 50 mg/kg body weight: ↓ p-p38 (Ahad et al., 2015).	↑ Nephroprotection, ↓ Blood glucose, ↓ Inflammation
	Caenorhabditis elegans *Pentagalloyl glucose 160 μM: ↑18% lifespan (Y. Chen et al., 2014)	Lung cancer cell (A549) 100 μM: ↓ p-p38, ↓ p-JNK (Park and Kim, 2013)	↓ Proliferation, ↑ Apoptosis, ↓ Antioxidant (GSH)
		Human glioblastoma U87 and U251n 30 – 40 μM: ↓ p-ERK (Lu et al., 2010).	↓ Cell viability, ↓ Proliferation, ↓ Invasion
		Human stimulated platelets 100 - 500 μM: ↓ p-p38 (Chang et al., 2012).	↓ Platelet activation, ↓ Platelet-leukocyte aggregation
		Stress-induced in rat pheochromacytoma (PC12) cell lines 1 μM: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (Huang et al., 2012).	↓ Inflammation, ↓ Oxidative stress
		The human nasopharyngeal carcinoma cells (NPC-BM1) 50 μM: ↓ p-p38 (Pang et al., 2017).	↓ Cell invasion, ↓ Migration
		LPS- stimulated microglial cells (BV-2) 1 μM: ↓ p-JNK (W.-H. Lin et al., 2015).	↓ Inflammation, ↓ Oxidative stress
		Human cervical cancer HeLa and HTB-35 cells 10 – 15 - 20 μg/mL: ↓ p-ERK (Zhao and Hu, 2013).	↓ Proliferation, ↓ Invasion, ↓ Angiogenesis

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Table 1 (*continued*)

IUPAC/Chemical Name	Experimental model, Dose and Effect on longevity	Experimental model, Dose and Effect on MAPK (ERK, p38, JNK)	Pharmacological effect
Genistein 5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one, is an isoflavonoid found in a number of plants, but soybeans and soy products like tofu and textured vegetable protein are the primary food source.	Caenorhabditis elegans 100 μM: ↑28% lifespan 50 μM: ↑10% lifespan (Lee et al., 2015).	d-Galactosamine-induced inflammation and hepatotoxicity in male Wistar rats 5 mg/kg body weight: ↓ p-ERK, ↓ p-p38 (Ganai et al., 2015).	↑ Hepatoprotection, ↓ Histological damage, ↓ Inflammation, ↓ Oxidative stress
		H_2O_2-induced cell death in primary rat cortical neurons 1 μM: ↓ p-ERK, ↓ p-JNK (Qian et al., 2015)	↓ Inflammation, ↓ Oxidative stress, ↓ Apoptosis
		VEGF- activated Human Umbilical Vein Endothelial Cells 100 μM: ↓ p-p38, ↓ p-JNK (Yu et al., 2012).	↓ Angiogenesis, ↑ Apoptosis
		Cardiac hypertrophy in C57/BL6 mice and phenylephrine-induced hypertrophy in neonatal rat cardiomyocytes 40 mg/kg body weight: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (*in vivo* Assay-Mice) 20 μM: ↓ p-JNK (in vitro assay –NRCM) (Meng et al., 2017).	↓ Endomyocardial fibrosis, ↓ Hypertrophic stimulation
		Lead (Pb)-induced toxicity in PC12 cell line 10 μM: ↓ p-ERK, ↓ p-p38 (Su et al., 2016).	↓ Apoptosis, ↑Antioxidant
		Non-alcoholic steatohepatitis-induced by high fat diet in male Sprague–Dawley rats 4 - 8 mg/kg body weight: ↓ p-JNK (Ji et al., 2011)	↓ Liver damage, ↓ Inflammation, ↓ Oxidative stress,
		PMA/A23187-induced mast cell activation (HMC-1 cells) 50 μM: ↓ p-ERK (Kim et al., 2014).	↓ Inflammation
Quercetin 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one, is a polyphenolic flavonoid widely distributed in many plants and fruits including red grapes, citrus fruit, tomato, broccoli and other leafy green vegetables, and a number of berries, including raspberries and cranberries.	Podospora anserine 300 μM: ↑10.2% lifespan (Warnsmann et al., 2018).	Chronic Prostatitis /Chronic Pelvic Pain Syndrome in Sprague Dawley rats 50 – 100 – 200 mg/kg body weight: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (Meng et al., 2018)	↓ Inflammation, ↓ Oxidative stress
	Caenorhabditis elegans 200 μM (quercetin-3-O-glucoside): ↑39% lifespan (Dueñas et al., 2013).	Adipogenesis induced by 3-isobutyl-1-methylxanthine and dexamethasone in pre-adipocyte cells 12.5 - 25 μM: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (Seo et al., 2015).	↓ Lipid accumulation, ↓ Obesity-induced inflammation
	Caenorhabditis elegans 100 μM: ↑11% lifespan 200 μM: ↑18% lifespan (Pietsch et al., 2009).	VEGF-stimulated Mouse cone photoreceptor-derived 661W cells 1.1 μM: ↓ p-ERK, 1.2 ↓ p-p38, ↓ p-JNK (Lee et al., 2017).	↓ Inflammation, ↓ Oxidative stress
	Drosophila melanogaster 1μM: ↑13% lifespan (Proshkina et al., 2016)	Liver injury induced by intraperitoneal injection of LPS (50 μg/kg)/D-GalN (300 mg/kg) in BALB/c Kunming species mice 50 – 100 mg/kg body weight: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (Peng et al., 2017).	↓ Apoptosis, ↓ Inflammation, ↓ Oxidative stress
		LPS-stimulated Myoblast rat H9c2 cells 10 μM: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (Gutiérrez-Venegas et al., 2017).	↓ Inflammation
		LPS-stimulated Murine macrophage RAW 264.7 cell line 50 μM: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (Cho et al., 2016).	↓ Inflammation
		Renal toxicity by Cisplatin-induced in Male Fischer F344 rats 50 mg/kg body weight: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (Sánchez-González et al., 2017).	↓ Cisplatin nephrotoxicity, ↓ Inflammation, ↓ Apoptosis, ↑Antioxidant
		Jejunum of pig stimulated after transport stress 25 mg quercetin per kg feed (as-fed basis):	↑ Intestinal health, ↓ Inflammation, ↓ Oxidative stress

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Table 1 (*continued*)

IUPAC/Chemical Name	Experimental model, Dose and Effect on longevity	Experimental model, Dose and Effect on MAPK (ERK, p38, JNK)	Pharmacological effect
		↓ p-ERK, ↓ p-JNK (Zou et al., 2016).	
Resveratrol 5-[(E)-2-(4-hydroxyphenyl)ethenyl]benzene-1,3-diol, is a plant polyphenol found in high concentrations in red grapes	Male C57BL/6NIA with high-calorie (HC) diet 22.4 ± 0.4 mg/kg body weight: ↓31% the risk of death from the HC diet (Baur et al., 2006).	IgE-sensitized rat basophilic leukemic RBL-2H3 cells 1 – 5 – 10 - 25 μM: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (Han et al., 2015).	↓ Allergic responses, ↓ Inflammation
	Nothobranchius furzeri 120 μg/g food: ↑33% lifespan 600 μg/g food: ↑56% lifespan (Valenzano et al., 2006).	12-O-tetradecanoyl-phorbol-13-acetate-treated human oral squamous carcinoma SCC-9 cells 75 - 100 μM: ↓ p-ERK 25 – 50 -75 - 100 μM: ↓ p-JNK (F.-Y. Lin et al., 2015).	↓ Metastasis, ↓ Migration
	Apis mellifera 30 μM: ↑38% lifespan 300 μM: ↑33% lifespan (Rascón et al., 2012).	Inflammation induced by free fatty acids in rat phaeochromocytoma PC12 Cells 5 - 10 - 25 μM: ↓ p-p38 (Xu et al., 2015).	↓ Inflammation
		TGF-β-estimulated osteoblast-like MC3T3-E1 cells 30 - 50 μM: ↓ p-JNK (Kuroyanagi et al., 2015)	↓ Inflammation, ↑ Sirt1 activity
		TNFα-induced injury in human umbilical endothelial cells 5 - 10 - 20 μM: ↓ p-p38 (Pan et al., 2016)	↓ Inflammation, ↑ Sirt1 activity, ↓ Oxidative stress
		Hypoxia-induced in microglial BV-2 cells 10 - 100 nM: ↓ p-ERK, ↓ p-JNK (Zhang et al., 2015).	↓ Inflammation, ↓ Oxidative stress, ↓ Microglial activation
		Oxidised low-density lipoprotein- induced apoptosis in RAW264.7 macrophages 100 μM: ↓ p-p38 (Guo et al., 2014).	↓ Apoptosis, ↓ Oxidative stress
		Diabetes-Induced Cardiac Dysfunction in Sprague–Dawley rats 80 mg/kg body weight: ↓ p-ERK, ↓ p-p38 (Gao et al., 2016).	↓ Diabetes-induced cardiac dysfunction, ↓ Inflammation
		LPS-induced BALB/c mice mastitis 10 – 20 - 30 mg/kg body weight: ↓ p-ERK, ↓ p-p38 (Zhang et al., 2017)	↓ Inflammation
Triptolide Trisoxireno(4b,5:6,7:8a,9)phenanthro(1,2-c)furan-1(3H)-one, 3b,4,4a,6,6a,7a,7b,8b,9,10-decahydro-6-hydroxy-8b-methyl-6a-(1-methylethyl)-, (3bS,4aS,5aS,6R,6aR,7aS,7bS,8aS,8bS), is a diterpenoid epoxide which is produced by the thunder god vine, *Tripterygium wilfordii*.	Drosophila melanogaster 0.05 μM: ↑8% lifespan in females; ↑20% lifespan in males (Danilov et al., 2015)	Cardiac remodeling in Wistar rats treated with isoprenaline 100 μg/kg body weight: ↓ p-p38 (Liu et al., 2015).	↓ Cardiac remodeling ↓ Cardiac fibrosis, ↑ Cardiac function
	Caenorhabditis elegans 50 μM: ↑51% lifespan (Gruber et al., 2007)	TNF-α-treated fibroblast-like synoviocytes from Rheumatoid arthritis patients 50 nM: ↓ p-JNK (Yang et al., 2016).	↓ Migration, ↓ Invasion
	Saccharomyces cerevisiae 10 μM: ↑70% lifespan (Howitz et al., 2003).	Brain of Alzheimer's disease APP/PS1 transgenic mice 20 μg/kg body weight: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (Cui et al., 2016).	↑ Learning, ↑ Memory, ↓ Aβ accumulation in the brain, ↓ Glial activation, ↓ Inflammation
	Caenorhabditis elegans 50 mg/L: ↑20.1% lifespan (S.-J. Kim et al., 2017)	Acute kidney injury cisplatin-Induced in male C57BL/6 mice 0.5 mg/kg body weight: ↓ p-ERK (H.-J. Kim et al., 2014).	↓ Blood urea nitrogen, ↓ Serum creatinine, ↓ Acute tubular necrosis
		Zymosan-induced inflammation in Human Corneal Fibroblasts 30 nM: ↓ p-ERK, ↓ p-p38, ↓ p-JNK (Liu et al., 2016).	↓ Inflammation

*6-hydroxydopamine (**6-OHDA**); Carbon tetrachloride (**CCl4**); Platelet derived growth factor (**PDGF**); Receptor activator of nuclear factor kappa-B ligand (**RANKL**); Bone Marrow Macrophage (**BMMs**); Nuclear factor-kappa B (**NF-κβ**); Vascular Endothelial Growth Factor (**VEGF**); Transforming growth factor (**TGF**); Nickel nanoparticles (**Ni NPs**); Lipopolysaccharide (**LPS**); Glutathione (**GSH**); d-galactosamine (**d-GalN**).*

downregulation of the PI3K/AKT pathway, which leads to promotion of senescence (increase expression of p53, p21 and p27) and suppression of tumorigenesis (Zhu et al., 2014). Moreover, it has been shown that endoplasmic reticulum (ER) stress and ER stress-associated unfolded protein response (UPR) reduced senescence in part through downregulation of ERK activity (Blazanin et al., 2017).

Analogous to p38 and JNK enzymes, strong experimental evidence suggests that ERK could have a key role in stimulating senescence and aging, but there is also evidence that ERK is relevant to controlling senescence and aging. Mice with depleted adenylyl cyclase type 5 (AC5 KO) increased longevity and stress resistance through upregulation of Raf/MEK/ERK activity and MnSOD, which results in protection against oxidative stress (Vatner et al., 2015). Moreover, in *C. elegans* MPK-1 (ortholog of mammalian ERK1/2) promotes longevity by stimulating the expression of SKN-1 and DAF-16 (Okuyama et al., 2010). In context of senescence, it has been reported that in senescent fibroblasts and hepatocytes from aging rats, the activity of ERK is downregulated (Lorenzini et al., 2002). UV radiation is a key risk factor in skin aging. Low-power laser irradiation (LPLI) has a protective effect on UVB-induced cell senescence. This protective effect is mediated by the upregulation of ERK activity, which contributed to decreased SA-β-Gal activity, p21 expression and G1 phase arrest (Ling et al., 2014). Moreover, using a rat model of aging (5% d-galactose s. c for 6 weeks), it was found that the reduction of ERK, Nrf2, and Cu–Zn SOD activity associated with age were enhanced by erythropoietin and inhibited by a selective inhibitor of ERK (PD98059) (Wu et al., 2017).

3. Natural product inhibitors of mapk enzymes (ERK, p38, JNK) with anti-senescence activity

Natural compounds with low toxicological profiles and enhanced pharmacological and pharmaceutical properties offer a potential source for screening and preclinical studies for aging and, possibly, other age-related pathologies, especially those without effective pharmacological therapies. Here, we selected several bioactive natural compounds and summarized experimental data showing both their positive effects on longevity and their MAPK enzyme inhibition (Table 1). For example: acacetin, baicalein, chlorogenic acid, epigallocatechin-3-gallate, fisetin, gallic acid, genistein, quercetin, resveratrol and tripotolide (Fig. 3). In general, in different experimental models these compounds can decrease the activity of ERK, JNK and p38, depending, of course, on cell type and environment and in response to the damage/injury contributed to decreased inflammation, mitochondrial dysfunction, apoptosis, necrosis or oxidative stress and those compounds that promote autophagy, tissue reparation and regeneration. Moreover, in cancer cells, MAPK enzyme inhibitors decrease proliferation, migration, invasion and metastasis, reduce angiogenesis/neovascularization and increase apoptosis. Furthermore, in context of metabolism, MAPK enzyme inhibitors reduce insulin resistance, blood glucose and dysfunction of glucagon secretion, decrease lipid accumulation and obesity-induced inflammation *(See more detail in* Table 1*)*.

Several natural bioactive compounds (e.g. polyphenols) contained in food, and able to modulate the senescence process, have recently been summarized by Gurau and colleagues. The authors also discussed how these bioactive compounds regulate the immune system and promote their anti-senescence effects through interaction with gut microbiota (Gurău et al., 2018). Interestingly, the natural bioactive compounds included in this review (acacetin, baicalein, chlorogenic acid, epigallocatechin-3-gallate, fisetin, gallic acid, genistein, quercetin, resveratrol and tripotolide) regulate MAPK enzymes, as well as reduce senescence and senescence-associated damage in different *in vivo* models of mammalian aging. For example, age-associated dysfunctions of the liver and senescence of liver cells contribute to acute liver failure. Using a D-galactosamine mice model of liver failure, it was found that acacetin reduced liver injuries by decreasing proinflammatory mediators (TNF-α and NF-κB), reducing phosphorylation of MAPK enzymes (ERK, JNK and p38), inhibiting TLR4 signaling and promoting autophagic flux (Cho et al., 2014). Baicalein diminished the senescence status of the senescence-accelerated mouse prone 8 (SAMP8) mice, in part, by decreasing proinflammatory cytokines and regulating intestinal microbiome (Gao et al., 2018). In D-galactose (D-gal)-induced accelerated aging rat model, baicalein decreased learning/memory decline and reduced the production of proinflammatory mediators (Duan et al., 2017). Senescence and uncontrolled inflammatory response aggravate cardiac damage during aging. Using a novel chlorogenic acid-phospholipid complex (CGA-PC) to improve its oral bioavailability, it was found that CGA-PC improved ischemia/reperfusion (I/R)-induced myocardial necrosis in SAMP8 mice by increasing anti-inflammatory cytokines, upregulating antioxidant enzymes and decreasing mitochondrial reactive oxygen species (mtROS) (Li et al., 2018). Moreover, CGA decreased D-gal-induced hepatic and renal injuries through upregulation of antioxidants and downregulation of pro-inflammatory cytokines (Feng et al., 2016). It is well-known that green tea extracts contain high levels of epigallocatechin gallate (EGCG). Using murine senescence SAMP8 model, it was reported that treatment with green tea extracts/EGCG reduced the muscle weight loss promoted by high-fat (HF) diets, in part, by improving on insulin sensitivity of skeletal muscle (Onishi et al., 2018). In D-gal-induced skin aging mice model, it was found that EGCG controls skin aging by avoiding the degradation of collagen fibers, increasing antioxidant enzymes and cell proliferation

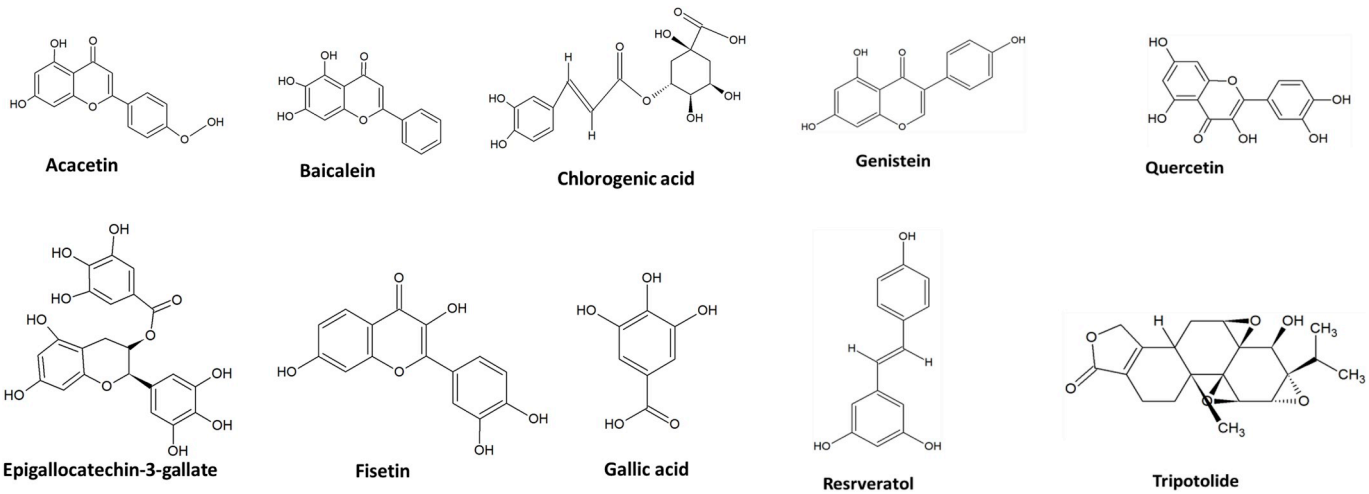

Fig. 3. Structures of the natural product inhibitors of MAPK

proteins, and decreasing senescence and pro-apoptotic related proteins (Chen et al., 2017).

In progeroid and aged wild-type mice, fisetin treatment promoted health-span through depletion of oxidative stress, senescence and senescence-associated secretory phenotype markers in fat, spleen, liver and kidney tissues (Yousefzadeh et al., 2018). Similarly, in SAMP8 accelerated aging mice model, fisetin increased cognitive function and locomotor activity, upregulated proteins associated with synaptic function and decreased stress and inflammation mediators (Currais et al., 2018). Finally, using D-gal induced aging rat and old-rat models, fisetin treatment promoted neuroprotection by downregulating oxidative stress markers, avoiding decrease of mitochondrial membrane potential, inhibiting apoptosis and promoting autophagy (Singh et al., 2018). Hallmarks of skin aging induced by environmental stressors such as UV is linked to accumulation of senescent cells and include wrinkle formation, dryness and thickening. Using a premature skin aging mice model, it was reported that gallic acid (GA) protected against UVB-induced skin damages in hairless mice *in vivo*. The authors suggest that this anti-aging effect of GA was linked to downregulation of matrix metalloproteinase (MMP-1) and upregulation of elastin, type I procollagen, and TGF-β1 (Hwang et al., 2014). Another model for aging research is SAMP mice, and treatment with GA improved antioxidant defenses (CAT and GPx) in 9-month-old SAMP mice (Li et al., 2005).

Accumulation of senescent cells promotes persistent inflammation and accelerates the aging process. Using old rats, it was found that age-related increases in NF-κB activity and expression of NF-κB-dependent proinflammatory genes were diminished by genistein (Kim et al., 2011). Impairment of immune response or immunesenescence is another hallmark of aging. High genistein intake lead to enhanced immune response in SAMP8 mice by decreasing proinflammatory mediators such as IL-2,-4,-10, IFN-gamma (Chan et al., 2009). Deterioration of cognitive and motor functions increase with age. Quercetin treatment recovered cognition in old rats through upregulation of SIRT1, tryptophan hydroxylase and tyrosine hydroxylase, as well as downregulation of NF-κB levels in hippocampus (Sarubbo et al., 2018). Using D-gal induced aging in mice, it was reported that treatment with quercetin improved learning and memory, in part, through induction of Nrf2 activity and its antioxidant target enzymes (HO-1 and SOD) (Dong et al., 2017). In triple transgenic Alzheimer's disease (3xTg-AD) old mice, quercetin decreased extracellular βA deposition, C-terminal APP fragments (β), βA 1–40 and βA 1–42 in hippocampus. Tau fibril formation was diminished and disrupted the formation of paired helical filament. Theses neuroprotective effect of quercetin resulted in better learning and memory functions (Sabogal-Guáqueta et al., 2015).

Aging contributes to impairment and decrease of physiological functions in most organ systems of mammalian spices. Interestingly, resveratrol (RSV) has shown evidence of protection against organ systems aging. For example, in old mice models, RSV decreased oxidative stress, inflammation, and fibrosis by inhibiting the renin-angiotensin system and inducing angiotensin 1-7/Mas receptor axis (Jang et al., 2018). RSV also contributed to decrease of different skeletal muscle histo-pathological conditions such as cross-sectional area, tubular aggregates, reduce inflammation marker (Cox-II), increase contractile features including myosin heavy chain IIB and sarco/endoplasmic reticulum Ca^{2+}-ATPase, and improve mitochondrial activity in tibialis anterior (Toniolo et al., 2018). Moreover, in old rats, RSV decreased the sarcopenia index, increased sarcomere length, I-band length and cross-sectional areas, upregulated anti-aging pathways (AMPK and SIRT1) and downregulated apoptosis (Liao et al., 2017). In old rats, RSV improved age-related cognitive functions by increasing antioxidant activity, short- and long-term memory as well as cytoarchitecture of the CA1 and CA2 regions in the hippocampus (Navarro-Cruz et al., 2017). Furthermore, in old mice, RSV protected liver against age-related inflammation by diminishing proinflammatory cytokines (IL-1β and TNF-α), NALP-3 inflammasome and Cox-II (Tung et al., 2015).

Hallmarks of AD, a pathological state linked to aging, include cognitive impairment, amyloid β (Aβ) peptide accumulation, increase of inflammation and oxidative stress. Using β-amyloid precursor protein (APP) and presenilin-1 (PS1) mice, it was reported that triptolide treatment improved learning and memory functions, reduced Aβ deposits and their production, decreased microglia activation and pro-inflammatory mediators (TNF-α and IL-1β), and upregulated antioxidant enzymes (Q. Wang et al., 2014).

Despite upregulation of MAPK enzymes in aging still being controversial, in this manuscript we show that moderate increase of the activity of these kinase enzymes promotes proliferation, differentiation, apoptosis and stress response. However, prolonged elevation of MAPK enzymes promotes senescence by increasing pro-inflammatory cytokines levels, as well as chronic low-grade inflammation observed with aging. Moreover, inflammation induces telomere dysfunction and accelerates aging (L. Wang et al., 2017), while dysregulation of MAPK enzymes signaling pathways are involved in age-related disorders. In fact, several bioactive natural compounds, that reduce MAPK activity, increase longevity in several organism model of aging (Table 1). Given the link between stress response, senescence and aging, it is possible that reducing aberrant MAPK activity may contribute, at least in part, to an extended life expectancy most likely by improving the stress response, decreasing inflammation and stimulating anti-aging pathways (AMPK, SIRT, FOXO). This information can be used for further design and synthesis of a novel series of selective MAPK enzyme inhibitors based on their analogues able to target mechanism of aging and age-related pathologies.

4. Limitations and future perspective

p38, JNK and ERK MAPK pathways are attractive drug targets for developing pharmacologic inhibitors, due primarily to uncontrolled modulation of MAPK signaling pathways that are associated with irreversible senescence, aging and age-related pathologies (Fig. 4). However, low specific activity and moderate toxicity are the major problems of MAPK inhibitors. Although most of the selected bioactive natural compounds in this manuscript decrease the activity of MAPK enzymes at different levels, some of them in certain types of cells increase MAPK activity. For example, acacetin in squamous cell carcinoma HSC-3 cells promote apoptosis through increasing activity/phosphorylation of ERK, p38 and JNK (C. D. K.-H. Kim et al., 2015). Baicalein promotes cell survival by increasing ERK/Nrf-2 activity in radiation-induced cell death in murine T cell lymphoma (Patwardhan et al., 2014). Epigallocatechin-3-gallate inhibits cell proliferation and migration, in part by activating p38 MAPK in the human ovarian carcinoma cell line (F. Wang et al., 2014). In tunicamycin-mediated cell death of the rat adrenal pheochromocytoma cell line, fisetin activates ERK, p38 and JNK, which induce adaptive cellular stress responses (Yen et al., 2017). Genistein promotes the activation of p38 and inhibit melanoma cell growth along with division through ER stress pathways (Heo et al., 2018). In LPS-stimulated BV-2 microglial cells, quercetin increases Nrf2/HO-1 activity under endotoxic stress through upregulation of ERK and p38 activity (Sun et al., 2015), and in human gastric adenocarcinoma cell lines. High doses (500 μM) of quercetin promote apoptosis by increasing activation/phosphorylation of ERK, p38 and JNK (M. C. Kim et al., 2014).

Moreover, elevated concentrations of bioactive natural compounds may not only cause and contribute to exacerbation of tissue damage but they also promote apoptosis, increase stress sensitivity, even genomic stability, which may lead to a shortening of the lifespan. In summary, while the pharmacological benefits of bioactive natural compounds on health are evident, they should not be used as a universal tool to improve human health. Technological advances in medicinal chemistry are allowing increased specificity and decreased toxicity of these kinase enzyme inhibitors, but targeting chronic pathologies requires long-term treatment, which often reduces efficacy and promotes toxicity. One vital challenge for the pharmaceutical industry is to improve the

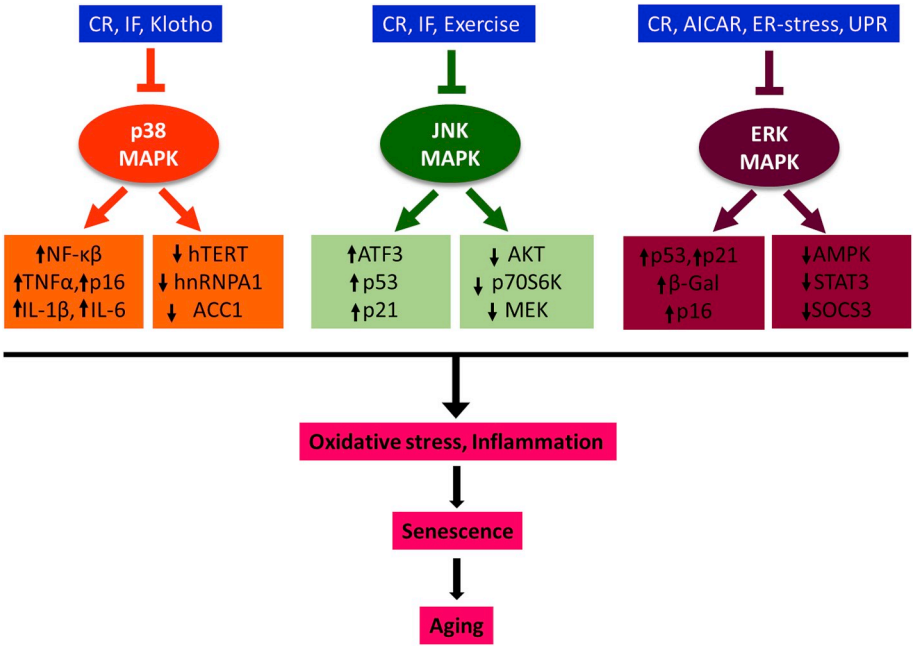

Fig. 4. Dysregulation of MAPK enzymes contribute to senescence and aging. Persistent activation of MAPK enzymes contribute to aging by increasing oxidative stress, inflammation and senescence. Interestingly, some anti-aging approaches such as caloric restriction and exercise decrease aberrant MAPK activity by improving the stress response, decreasing inflammation and senescence markers. Nuclear factor-kappa B (**NF-κβ**); Transforming growth factor (**TGF**); human telomerase reverse the transcriptase (**hTERT**); Heterogeneous nuclear ribonucleoprotein A1 (**hnRNP A1**); Acetyl-CoA carboxylase 1 (**ACC**1), Activating transcription factor 3 (**ATF3**); β-galactosidase (**β-gal**), AMP-activated protein kinase (**AMPK**); Signal transducer and activator of transcription 3 (**STAT3**); Suppressor of cytokine signaling 3 (**SOCS3**); Caloric restriction (**CR**); Intermittent fasting (**IF**); Adenosine analog that selectively activates AMPK (**AICAR**); Unfolded protein response (**UPR**); Endoplasmic reticulum (**ER**).

properties of kinase enzyme inhibitors.

Finally, most of the evidence showing that natural bioactive compounds included in Table 1 promote longevity (increase lifespan) and were performed in non-mammalian model organisms. Although these compounds are promising because of various higher vertebrate rodent aging models (mice and rats) most of them decrease senescence and senescence-associated damage. Specific experiments using additional mammalian model organisms to study whether interventions with these compounds extend lifespan are needed to confirm their potential pro-longevity effect.

5. Conclusions

Upregulation of MAPK enzymes in aging are tissue/cells specific and depending on sex, age and species of the experimental animal model used. However, the fact that several natural product compounds can both increase longevity and decrease MAPK enzyme activity, may prove an excellent tool for the pharmaceutical industry to design and synthesize a novel series of selective MAPK enzyme inhibitors. Based on selected bioactive natural product compound analogues, improved combination therapies with anti-aging effects even to combat aging at the tissue level could be expected.

Although more studies using additional aging models are needed, we suggest that these selected natural bioactive compounds that regulate MAPK enzymes and reduce senescent cells can potentially be used to improve longevity and prevent/treat age-related diseases.

The combination of anti-aging drugs with nutritional approaches, including bioactive natural compounds able to increase longevity, could be a possible strategy for improving the efficacy of anti-aging therapies. Approaches to diminishing the toxicity of bioactive natural compounds without affecting their anti-aging (anti-senescence) effectiveness are essential for improving the pharmacotoxicological profile of these potential new anti-aging drugs.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

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Transparency document

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