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Review

Targeting miRNAs by polyphenols: Novel therapeutic strategy for aging

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ABSTRACT

Regarding the importance of genetic and epigenetic factors in regulation of aging process, different expression pattern of non-coding RNAs in aging could be investigated. Accordingly, micro RNAs (miRNAs) with a wide range of physiological functions as well as a significant footprint in many diseases have been demonstrated to be down or upregulated during the aging process. Therefore, age-associated microRNAs and their targets have potentially detected the accelerated aging and predicted the risks for age-related diseases. Polyphenols as important antioxidants in human dietary observed in fruits and some beverages have beneficial effects on longevity and aging. Considering miRNAs as an interesting mediator in modulating polyphenols' biological effects, targeting miRNAs which is using polyphenols could be a novel strategy for aging.

1. Introduction

Aging is a time-dependent and integrated gradual deterioration of cellular activities that leads to an increased risk of cell death and a risk factor for human pathologies such as cancer, diabetes, cardiovascular disorders and neurodegenerative diseases [1] with an effect to the entire organism. Though, these effects have not covered all types of cells, tissues and organs have been affected in a similar ratio [2]. Aging phenotype and longevity in human could be the result of multifactorial processes, including an interaction between genetics, environmental factors and stochasticity contributed to overall presentation of aging phenotype [3]. Delaying the onset of aging has been attributed to substantial improvements in the current healthcare system. Currently, maximum life expectancy is averagely 80 years, adding that the number of individuals above 65 years old has been doubled since 1960s [4]. According to the report of health organization (2015), 60% of 57 million deaths are due to non-contagious diseases around the world [5]. Considering the aging alterations and its complication(s) in human and other species, the role of miRNAs has been known as a mediating complex and interconnected pathways. In this case, miRNAs have a role in aging like other pivotal cellular processes such as aging-related diseases, cellular and organismal aging [6]. Polyphenols are one of the most important antioxidants in human dietary seen in fruits and some of beverages, carrying the beneficial effects on longevity and aging [7]. miRNAs as an interesting mediators in modulating polyphenols' biological effects [8] and targeting the miRNAs that apply polyphenols could be a novel and promising strategy for aging.

1.1. Mechanisms of aging

Aging is a natural phenomenon described by a progressive deterioration of cellular processes in all tissues. Age-related changes are numerous and are considered as an inseparable part of almost every cellular and biological function pathway [1]. Several theories of aging have been confirmed as a hallmark of aging including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication [1]. Besides, caloric restriction (CR) is widely accepted for health development and longevity extension [9]. Mondal et al. (2014) has described two types of aging process as "programmed aging" and "wear and tear aging". Programmed aging refers to a specific regulatory

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program, considering the aging genes that control the entrance to other life-stages [10]. However, wear and tear aging is affected by environmental factors such as exposure to radiation, toxins, reactive oxygen species ROS, glycation, metal ions, and etc. [10]. Many proposed cellular signaling pathways are associated with aging such as nutrient sensing systems including Mammalian Target of Rapamycin (mTOR) as a sensor of high amino acid concentrations, insulin and insulin-like growth factor (IIS) pathway that participate in glucose sensing, AMP-activated protein kinase (AMPK) which senses low energy conditions through detecting high AMP levels, and sirtuins which sense low-energy conditions through detecting high NAD^+ levels [1,11]. Indeed, the current data has strongly supported the idea that nutrient sensing systems involved in anabolic signaling (mTOR, IIS pathway) accelerates the aging process, however, other two nutrient sensors as AMPK and sirtuins act in contrast to IIS and mTOR. It means that these signaling pathways are involved in catabolic signaling instead of nutrient abundance and anabolism. Therefore, their upregulation contributes to healthy aging [1]. The most common theories about the aging are the accumulation of mitochondrial DNA (mDNA) damage. These processes have led to mitochondria dysfunction during the time that automatically generates reactive oxygen species (ROS) as highly responsible aging. Also, respiratory chain dysfunction increases different types of aging phenotypes [12]. Klotho is an enzyme that is encoded by KL gene in human including two forms: 1) transmembrane that functions as a co-receptor for fibroblast growth factors (FGF23) and modulates phosphate, calcium and vitamin D metabolism and 2) secreted form of this protein that controls several ion channels and signaling pathways including insulin, IGF-1 and Wnt which is potentially involved in biology of cancer and stem cells [13]. While the downregulation of KL gene can obviously accelerate aging, the overexpression of this gene postpones the aging process [10]. Indeed, klotho gene is known as an aging suppressor that accelerates aging process when defected and increased longevity on overexpress [14] (Fig. 1).

1.2. Aging and age related diseases

Aging is the most important risk factor for developing a large number of diseases, ranging from cancer to neurodegenerative disease [15]. The age-related diseases generally consider a chronic and loss-of-function disease. These diseases are accompaniment with loss of cells, cellular and subcellular function, tissue components and normal cellular or tissue function. Some of these pathologies include many neurodegenerative diseases, multiple states of cardiovascular disease, macular degeneration, osteoporosis, sarcopenia and etc. [15]. Neuro-Degenerative Diseases (NDDs) are highly prevalent among elderly people which are developed with age. Specific areas of central nervous system (CNS) demonstrate different vulnerabilities to aging and multiple age-related NDDs [16]. Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) selectively target defined subpopulations of neurons, leading to the ranges of molecular and pathologic features. All of these diseases contribute to aging as the main risk factor. Indeed, age-related NDDs can be partly considered as a form of accelerated aging [17]. Progressively, the inflammation is associated with aging and chronic disease. Indeed, the basic inflammatory response increases with age and related to neurodegenerative diseases [18]. Accordingly, inflammatory cytokines derived from innate immune response are induced by enhanced production of accumulating beta-amyloid (Aβ) in neuro-degenerative diseases such as Alzheimer [19].

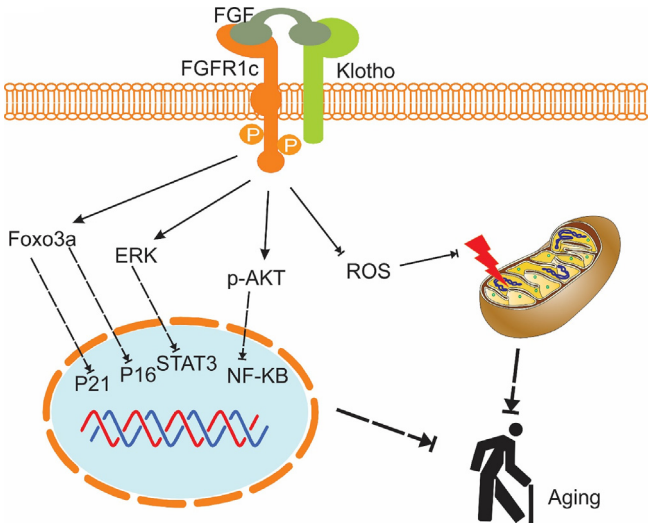

Fig. 1. By overexpression of KL gene, Klotho protein as a co-receptor for FGF23, caused anti-oxidant capacity of cell increased and inhibition of mtDNA damage occurred. Also some active signaling pathways and molecule by Klotho protein as an aging suppressor, lead to longevity of cell.

Diabetes is one of the most important and prevalent diseases of adults. Thus, diabetes type2 (T2DM) is seen in arteries, eyes, and kidneys. These pathologies are linked to an inflammatory process overstates by the presence of Advanced Glycation End (AGE) production led to overproduction of reactive oxygen species (ROS). Diabetes is considered as a risk factor for disruption in several neuro-psychological functions. Indeed, protein glycation and increased oxidative stress are two major mechanisms associated with biological aging [20]. Atherosclerosis is a classic inflammatory disease which is extremely common in elderly ages including a life-long process that begins in young ages, but clinically manifests at older age. Against to the belief that cellular senescence is associated with atherosclerosis, there is a growing evidence that cellular senescence elevates atherosclerosis [21].

2. MicroRNAs

MicroRNAs (miRNAs) are short non-coding RNAs (ncRNAs) molecules with a pivotal role in post-transcriptional regulation of gene expression. Lin-4 as the first miRNA is detected in C. elegans (1993) is not translated to protein [22], then a few years later miRNA let-7 is identified [23]. These gene regulators are associated with an extensive range of cellular processes such as cell proliferation, differentiation, and apoptosis by binding to 3′ untranslated regions (UTR) of their target transcripts that leads to silencing the gene expression through mRNA degradation or translational blocking [24]. miRNA binding is conducted via complementarity to the “seed” sequence of miRNA, which is the trace of 7–8 nucleotides at 5′ end of miRNA molecule with a complementary sequence into target mRNA [25]. Since the length of miRNAs are short (~19–24 nucleotides), a single miRNA can be binded with more than 1000 different mRNAs, thereby concurrently modulating several signaling pathways [23]. miRNAs estimates to modulate as many as 60% of all human mRNAs that demonstrate all the cellular and molecular functions [26]. miRNAs have been observed in a wide range of living things, including plants, green algae, viruses and more greatly in animals. These small molecules are also associated with both normal and disease states, such as cancer and cardiovascular diseases [25], suggesting that, though MicroRNAs are small molecules, they have a big role in cellular function.

3. Role of miRNAs in aging

Multiple molecular mechanisms are involved in aging modulation, thus miRNAs as new research fields have been generated. These molecules has been increasingly become interesting due to their ability to affect all the aspects of aging [27]. Aging in humans and other species occurs with continuous shortening of telomere repeats at the end of eukaryotic chromosomes. Telomeres are protected through the binding of a complex protein such as TRF1 and TRF2 [28]. In this case, several

miRNAs are involved in telomere maintenance. Thereafter, miR-155 could be the target of TRF1 gene [28] also, telomerase transcripts TERT are attacked by miR-38 in human anaplastic thyroid carcinoma cell lines [29]. miR-34 is one of the other regulators of telomere length that linked to telomere length in some gall bladder adenocarcinoma [30]. As mentioned above, altered expression of miRNAs during aging can affect the expression of telomeric constituents and cellular lifespan, respectively. According to the evidence, there is a complex interaction between epigenetic changes and miRNAs during the aging. Like mRNAs, the expression of miRNAs is influenced by epigenetic alterations such as DNA methylation. For example, it is observed that miR-127 in the presence of 5-aza-2′-deoxycytidine or 5-aza-dC as a DNA methyltransferase inhibitor is increased in bladder carcinoma cells line [31]. Subsequently, miR-124 and miR-203 in the presence of this inhibitor are elevated in hepatocellular carcinoma [32]. Also, decrement in the expression of miR-200 and miR-141 via DNA methylation or histone modifications is obvious [33]. Obviously, any alteration expression of these miRNAs might be an interpretation for alterations in DNA methylation which is detected during the aging. Aging is widely known to be the result of mitochondrial damage. Some miRNAs are capable to modulate aging through the regulation autophagy of mitochondria [34]. It has been reported that a few numbers of miRNAs including miR-210, miR-486-5P, miR-494 and miR-542-5P presumably regulate autophagy by a mTOR dependent mechanism [35]. As a result, based on the data, miRNAs are promising sensors of aging and cellular senescence by affecting genetic – epigenetic and other cellular processes.

4. Polyphenols: natural chemicals with therapeutic potential

Polyphenols are structural organic compounds characterized by the existence of multiple phenolic groups in their structure. Also, they are originally made by plants and found in their seeds, stems and virtually every part, however, made as semi-synthetic and synthetic compounds [36]. Polyphenols are structurally categorized to subgroups of hydroxybenzoic acids, hydroxycinnamic acids, flavonoids, stilbenes and lignans. Flavonoids are the largest and probably most important group of polyphenols categorized to flavonols, flavones, isoflavones, flavanones, anthocyanidins and flavanols [37]. Based on the structure(s) and number of phenolic groups, polyphenols exhibit a wide range of chemical characteristics such as oxygen radical scavenging and numerous interactions with other molecules existent in food sources [38]. Because of the abundance of polyphenols in natural food sources, they are used in traditional medicine industry [39], and currently considered in multiple human pathologies including neurodegenerative diseases, cancers, inflammatory diseases, cardiovascular conditions, and metabolic diseases [40]. Polyphenols are used in vitro and in vivo studies and more clinical trials are recently conducted [41]. Polyphenols exert their effects by several mechanisms, say they can modulate important signaling pathways involved in numerous cellular functions such as AKT/PI3K signaling, NF-KB signaling, ERK signaling, multiple growth factors associated with signaling pathways, and others [42–45]. Polyphenols have also direct and indirect anti-oxidant effects, enabling cells to reduce damage(s) caused by ROSs [46]. Furthermore, polyphenols exhibit functions that are not directly related to their effect on oxidative balance of cells including inhibition of angiogenesis, inhibition of histamine release, Inhibition of leukotriene B4 release, SIRT1 activation, FAS inhibition and activation of Gluconeogenesis [47].

5. Beneficial effects of polyphenols in aging related diseases

5.1. In neurological diseases

Neurodegenerative diseases are closely linked to aging process while mostly happen in elderly. The constant creation of ROSs, increased inflammatory responses and the resulting induction in apoptosis or autophagy responses render the neurons susceptive to functional decline, which is obviously seen in Alzheimer, Parkinson and many more [48]. A review by Syarifah-Noratiqah et al. has suggested three polyphenolic compounds including Curcumin, Resveratrol and Epigallocatechin-3-gallate as favorable options for Alzheimer treatment [49]. In this realm, similar results have been reported by Colizzi, though, further evidence is needed to suggest polyphenols as routine treatment options [50]. It is suggested that polyphenols exert their effects on Alzheimer by Amyloidogenesis reduction, and reduction in inflammation, sparing neuronal cells with established amyloid deposition [51]. Also, deposition of amyloid particles activates signaling pathways such as NF-κB/IL-1β/ NLRP3 signaling is inhibited by polyphenols [52,53]. Parkinson's disease is another neurocognitive disorder characterized by deposition of α-synuclein, contributing to progressive neuron loss in substantia nigra led to dopamine output reduction [54]. A study by Roy et al. has suggested that epigallocatechin-3-gallate suppresses the formation of γ-Synuclein fibrils by binding to nucleus forming oligomers of γ-Synuclein while negatively affecting fibril nucleation [55]. Agents such as Curcumin and Epigallocatechin gallate interrupted ERK and NF-KB signaling has protective effects in Parkinson's model [56]. Huntington's chorea is another degenerative disease characterized by huntingtin mis-folding and rapid decline in motor and mental function. Studies have shown that epigallocatechin-gallate is able to enhance motor function in models of Huntington's disease by reducing polyglutamine (polyQ) toxicity [57]. On the other hand, Wang et al. has shown that grape polyphenols are able to stop the process of polyQ aggregation in phaeochromocytoma (PC)-12 cell line [58]. Pasinetti et al. has suggested that Resveratrol could have beneficial effects on Huntington's disease and diabetes [59] (Fig. 2).

5.2. In age-related cardiovascular malfunctions

Aging is coupled with many cardiovascular pathologies, including alterations in the anatomy and function of heart and vessels, ischemic heart disease, atherosclerosis, heart failure and degenerative changes of vessels [60,61]. Numerous polyphenols such as resveratrol protect myocytes from ischemic injury and improve cardiac function after ischemia have been studied [62,63]. Sung et al. has shown that Resveratrol improves cardiac function after heart failure and reduces the symptoms of low ejection fraction being caused by ischemia [64]. Also, polyphenols are beneficial in preventing the occurrence of changes because of hypertension and diabetes in vascular system. Diabetes is contributed to the progression of inflammation in vessels while causing damage to endothelium via advanced astrocyte elevated gene (AEG) products [65]. On the other hand, hypertension causes great distress for cardiovascular system, due to its great contribution to ischemic heart disease and heart failure. It's also involved in pathologies of different size vessels, causing the formation of atherosclerotic plaques, aneurysms and pathologic changes in vessel anatomy. A study by Cheng et al. has shown that anti-oxidative capabilities of polyphenols has greatly reduced superoxide production, creation of arteriosclerotic plaques and platelet aggregation while improving oxidative stress situation of mitochondria and enhancing the lipid profile [66]. Another study by Al Hroob et al. has suggested that epigallocatechin-3-gallate is able to ameliorate the negative effects of diabetic cardiomyopathy. Other studies have also suggested that polyphenols found in red wine and green tea can ameliorate the negative effects of ischemia reperfusion on myocytes [67,68].

Polyphenols are also able to partially ward off the negative effects of cardiac hypertrophy. It is shown that blueberry leaf extract which contains high amounts of polyphenols is useful in preventing the negative effects of isoprenalin caused cardiac hypertrophy, enzyme leakage from cells, and electrocardiogram changes. This extract modulates the expression and signaling of mediators such as NF-κB, COX-2, TNF-α and IL-6 to achieve this. Blueberry extract also reduces the fibrotic reaction caused because of isoprenaline by inhibiting high levels of TGF-B. Similar results have been shown for Roselle Extract in

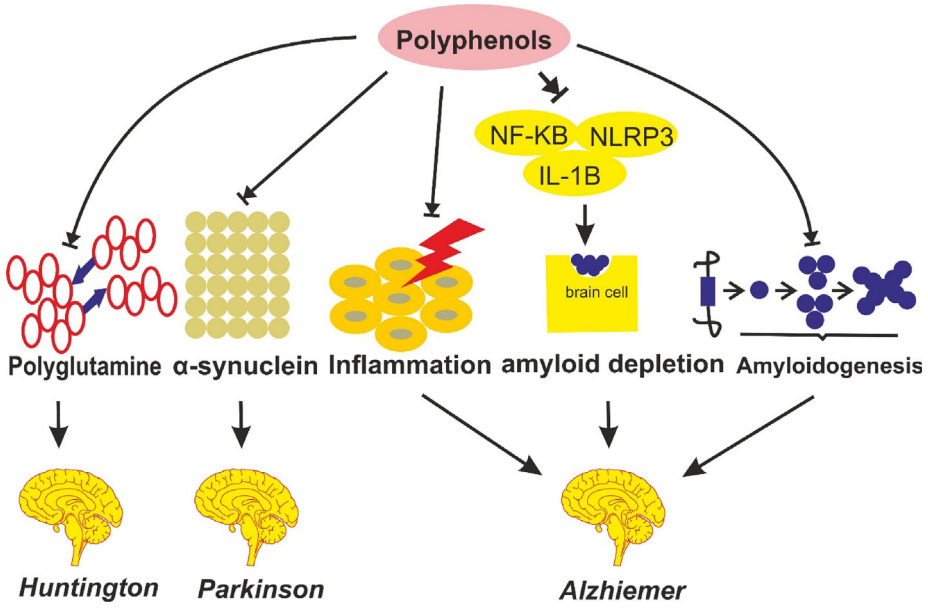

Fig. 2. The schematic diagram provided reveals the useful and treatment effects of Polyphenols administration on neurodegenerative disease, according to this schematic representation Polyphenols substances can reduce horrible effects of the Alzheimer, Parkinson, and Huntington.

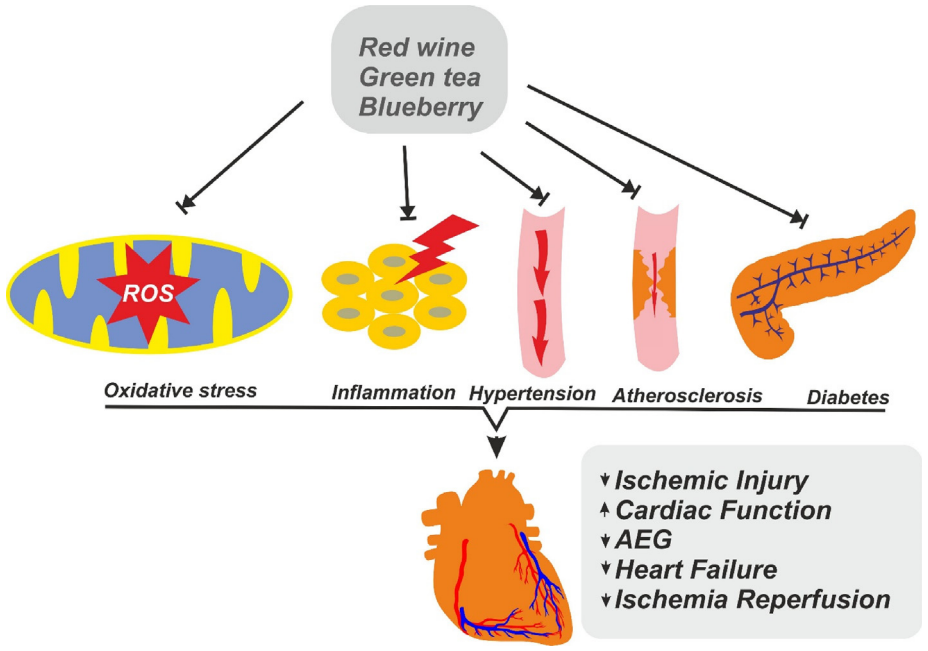

Fig. 3. The figure given shows the beneficial effects of Red wine, Green tea and Blueberry as purified polyphenol substances on heart by treatment effects on diabetes, atherosclerosis, hypertension, inflammation and oxidative stress.

decreasing isoprenaline induced fibrosis by Ali et al. Interestingly, Saliba et al. has shown that polyphenols could also contribute to the reduction of fibrosis via targeting transient receptor potential canonical 3 (TRPC3) channels, and the fact that this function is not solely depended on the reduction of inflammation by acting as a ROS scavenger (Fig. 3).

5.3. In age-related inflammatory diseases

According to literature, aging is linked to chronic inflammation, because of chronic infections, cellular senescence, obesity, cellular debris and traumatic experiences, which increase the likelihood of inflammation linked diseases. Furthermore, these phenomena contribute to cellular damage and aging as well [69,70]. Chronic inflammation is linked with multiple pathologies including rheumatologic conditions, cancers, osteoporosis, and mood disorders [71-73]. One strategy to stop this delirious cycle is the use of natural compounds to control inflammation. Some studies have suggested that in polyphenols like Nanocurcumin, Epigallocatechin Gallate, curcumin, Resveratrol suppress the inflammation by affecting inflammatory signaling pathways [74-76]. One mechanism by which polyphenols inhibit inflammation is by affecting the NF-KB signaling pathway. One study has reported that Genistein inhibits the NF-KB pathway by promoting AMPK activation [77]. Furthermore, polyphenols inhibit the increased expression of interleukins and matrix metalo-proteinases after the activation of upstream inflammation regulators such as NF-KB [78]. Polyphenols also inhibit the production of ROSs, which are important effectors of damage caused by inflammation [79]. Polyphenols may modulate the

function of enzymes such as COX1, COX2 and LOX, which are responsible for the production of increased oxidative stress in tissues [80].

6. Targeting miRNAs by polyphenols: novel therapeutic strategy for aging

6.1. Polyphenols and diabetes: microRNA interaction

Aging is characterized by numerous changes in normal physiological functions including glucose metabolism. Studies have shown that aging contributes to insulin resistance by multiple mechanisms such as reduced secretion of insulin and post-receptor defects in target cells, and in return, insulin resistance and intolerance to glucose contributes to degenerative changes in multiple tissues including kidneys, peripheral nervous system, vessels and eye [81]. A study by Ohno et al. has shown the administration of Apigenin to transgenic mice in which overexpressed miR-103 has resulted an increased tolerance to glucose by decreasing fasting blood glucose levels and reducing adipocytes' size. This effect is shown to be mediated by the negative effect of Apigenin on miRNA maturation and function. This polyphenol decreases the signaling output of mitogen-activated protein kinase (MAPK), which has important roles in phosphorylating TRBP (RISC-loading complex subunit), and enhances the maturation of miRNAs by promoting stabilization in microRNA-generating complexes. Furthermore, Apigenin reversed the functional effects of miR-103 on caveolin-1 as a regulator of the insulin receptors [82]. Another study by Otton et al. has suggested that green tea polyphenols are able to decrease adipose tissue size and limit weight gain in mice that is under a high-fat diet. It is associated with decreased expression of miR-335 in adipose tissue, which is initially upregulated before treatment in response to an increased inflammation. Thus, it is postulated that green tea polyphenols also decrease inflammation, and by limiting the inflammatory response, insulin sensitivity is raised through inhibition of TNF-α functions. Accordingly, TNF-α suppresses the genes in signaling of insulin and lipid metabolism [83]. Yang et al. has found that Isoliquiritigenin and Liquiritigenin are able to increase the amount of miR-122 in hepatic cells of mice undergoing a high-fat diet by inhibition of JNK signaling because JNK in the absence of these Polyphenols compound provides inactivation of hepatocyte nuclear factor 4α (HNF4α) which is the main responsible for miR-122 expression and leads to the induction of protein tyrosine phosphatase 1B (PTP1B) as a negative regulator of microRNA. This is important because miR-122 is an abundant miRNA in liver tissue. Respectively, the literature has shown that it has an essential role in reducing resistance to insulin in hepatic tissue [84]. Another miRNA with a pro-insulin role is miR-205. miRNA prevents the apoptosis of pancreatic beta cells induced by tumor necrosis factor-alpha, and further exerts functional roles by downregulating NF-KB signaling pathway and increasing Akt/PI3K. You et al. has shown that Baicalin, a flavonoid found abundantly in Scutellaria Baicalensis, increases the amount of the aforementioned microRNA while promoting normal pancreatic beta-cell function [85]. Qin et al. has suggested that 3-O-[(E)-4-(4-cyanophenyl)-2-oxobut-3-en-1-yl], a kaempferol (Fla-CN), a semi-synthetic flavonoid is able to up-regulate miR-27 and activate AMPK which is resulted in insulin sensitivity increment and body fat percentage decrement and enhanced the metabolic profile of rats which is undergoing a high fat diet [86].

6.2. Polyphenols and antioxidant property: microRNA interaction

Likewise, Jeon et al. has found that the use of Fisetin harbored the same benefits, because its treatment causes a reduction in the expression of miR-378, which is increased after a high-fat diet. Treatment with Fisetin has resulted a reduced hepatosteatosis and modulation in lipid metabolism [87]. Zhao et al. has experimented Polydatin, a precursor form of resveratrol, to study its effects on lipid metabolism and inflammation in liver. They induced inflammation in the livers of Sprague-Dawley rats by feeding them a high fructose diet, and then treated them with the aforementioned polyphenol. They found that treatment has increased the amounts of miR200a led to a decrease in negative regulatory role of Kelch-like ECH-associated protein 1 (Keap1) on nuclear factor erythroid 2-related factor 2 (Nrf2), which is resulted in anti-oxidative capacity increment of cell, and lipid deposition decrement in liver cells [88]. In another study, D'Amore et al. has studied the effect of dietary intake of extra virgin olive oil (rich in polyphenols), on insulin resistance and peripheral blood mononuclear cells (PBMCs) of patients previously diagnosed with metabolic syndrome and healthy subjects. it's found that this supplementation has resulted a switch in PBMCs that make them less prone to significant inflammatory responses, and also induced enhancement in glycemic profiles of the subjects. These effects are the greatest in healthy population compared to those with preexisting metabolic syndrome [89]. Another important issue related to aging is osteoarthritis caused by wear and tear of musculoskeletal system and characterized by long-standing mechanical degeneration of joint and its supporting structures, chronic inflammation and a continuing degenerative process [90]. This inflammatory response is driven by many mediators including interleukins, and most importantly interleukin-1 [91]. A study by Rasheed et al. has found that Epigallocatechin-3-O-gallate exerted its anti-inflammatory and anti-arthritic effects by suppressing microRNA machinery in chondrocytes, and inhibited the interleukin-1 dependent expression of ADAMTS5 as a key effector enzyme in osteoarthritis [92]. In another study, they have suggested that Epigallocatechin-3-O-gallate is also able to increase the expression of some microRNAs in chondrocytes (Rasheed et al., when). They found that some microRNAs such as miR-199a-3p exerted protective effects against inflammation and degeneration by limiting the expression of cyclooxygenase (COX)-2 and production of prostaglandin E2 (PGE2) and these microRNAs are readily inhibited by the singling that is initiated and maintained by interleukin-1. Epigallocatechin-3-O-gallate upregulated miR-199a-3p and thus reversed the effect of interleukin-1 [93].

6.3. Polyphenols hearth, kidney and skin: microRNA interaction

Another important change occurring in aging process is the vascular system change followed by ischemic changes in kidneys, heart and brain [94]. Bian et al. has found that Luteolin, a flavonoid found in many food sources, inhibited the injury that occurred by the ischemia–reperfusion in myocytes after an episode of infarction. The mechanisms underlying this type of injury include the ROS production increment after reperfusion and inappropriate contracture of myocardium that is resulted from an overload of calcium ions [95,96]. Luteolin is able to limit this kind of injury by inhibiting the expression of miR-208b-3p expression led to a reduced apoptosis in myocytes. Furthermore, treatment increases the expression of Ets1 as a direct target of miR-208b-3p [97]. Aging affects the renal system by multiple alterations in vascular system contributed to both fibrotic changes in kidney and a chronic reduction in glomerular filtration rate, which is a hallmark of aging and its associated chronic kidney disease [98]. Studies have suggested that fibrotic changes in kidney greatly enhance the rate at which chronic kidney diseases lead to chronic kidney failure, thus it is suggested that stopping the process of fibrosis could enhance kidney function. Wu et al. has suggested that the use of total flavonoids extracted from Carya Cathayensis leaves ameliorated renal fibrosis. Further investigation have shown that administration of these flavonoids reduced the expression of fibrotic markers, and increased the expression of miR-21 led to an increased expression of Smad7 [99]. Also, Smad7 is a potent anti-fibrotic mediator which suppresses renal fibrosis by effecting the TGF-β/Smad3 signaling [100]. Exposure to ultraviolet (UV) radiation, resulting to degenerative changes in skin which leads to premalignant and malignant lesions is another hallmark of aging and its effect on body systems. Lee et al. has examined the

Table 1
Anti-aging effects of polyphenols by targeting miRNAs.

Polyphenol agents	Target miRNAs	Target molecules and cells	Anti-aging effects	Experimental models	Ref
Apigenin	↓miR-103	MAPK and caveolin-1	↑effect on insulin receptors ↑ insulin uptake	Mice	[82]
Green tea polyphenols	miR-335↓	Adipose tissue TNF-α	Inflammation ↑ insulin sensitivity	Mice	[83]
Isoliquiritigenin and liquiritigenin	↑ miR-122	Hepatic cells HNF4α	↓ JNK signaling ↓ induction of PTP1B	Mice	[84]
Baicalin	miR-205↑	Pancreatic beta cells NF-KB Akt/PI3K	↓ TNF-α NF-KB↓ Akt/PI3K↑	Pancreatic β-cell line Min6	[85]
Kaempferol (Fla-CN)	miR-27↑	AMPK Leptin Adiponectin	↑ insulin sensitivity ↓ body fat percentage	Mice	[86]
Fisetin	miR-378 ↓	adipose tissue NRF-2	hepatosteatosis↓	Mice	[87]
Polydatin	miR-200a ↑	Keap1 and Nrf2 of liver cells	↑ anti-oxidative capacity	Rat	[88]
Epigallocatechin-3-O-gallate	↑ miR-199a-3p	(COX)-2 of chondrocytes	↓ inflammation and degeneration	Human	[93]
Luteolin	↓ miR-208b-3p	Ets1 in myocytes	↓ apoptosis	Rat	[97]
Carya Cathayensis flavonoids	miR-21↑	Smad7 of renal cells	renal fibrosiss↓ ↑ TGF-β/Smad3 signaling	Mice	[99,100]
Troxerutin	↑ miR-205-3p miR-21-3p↑ ↓ miR-513b miR-483-5p ↓	HaCaT keratinocytes	↑ DNA damage response DNA repair↑	HaCaT keratinocyte cells	102
Epigallocatechin-3-O-gallate	↑ miR-133a/b	Benign prostatic hyperplasia	Angiogenesis↓ ↓ Smad3 signaling ↓ inflammation ↓ proliferation fibrosis↓	Rat	[106]
Epigallocatechin-3-O-gallate	miR-21↓ miR-330↑	Androgenic receptors	Proliferation↓ ↑ Suppression of tumor	LNCaP cell line	[107]
Luteolin and gefitinib	miR-630 ↑ miR-570 ↑	Prostatic cancer cell	↓ GAK expression cell death ↑	PC-3 cell line	[108]

effects of Troxerutin on human HaCaT keratinocytes undergoing UVB administration, resulting that pretreatment of these cells with troxerutin (up to 10 μM) upregulated microRNAs such as miR-205-3P, miR-21-3p, and downregulated ones such as miR-513b, miR483-5p and more. These alterations are coupled by an increase in DNA damage response (DDR) and DNA repair, resulting apoptosis reduction in response to UV radiation [101]. Another study by Lim et al. has suggested that troxerutin has beneficial effects in reversing the oxidative damage implicated to dermal papilla cells by H2O2 administration. Likewise, 24 microRNAs are differentially expressed after troxerutin administration, especially those involved in MAPK and WNT signaling pathways which is coupled with increased resistance towards ROSs generated by H2O2 [102]. Further investigation regarding the beneficence of polyphenols in skin conditions has shown that epigallocatechin-3-gallate is also an effective agent. An et al. (when) has found that the supplementation of human dermal fibroblasts treated with UV radiation has caused an expression of microRNAs increment such as miR-1246, miR548c-3p, mi-R636 and mi-R933. These microRNAs targets molecules such as BCL-2, FOXO1, NFKBIA, SMAD3, TGFBR2 involved in cell survival, proliferation and other basic functions. Moreover, specific miRNAs where repressed and targeted molecules such as SIRT1 and PTEN are involved in aging process. The cumulative effect of all these alterations is an increased resistance towards UV radiation and increased cellular viability, which are achieved by low and non-toxic concentrations up to 50microMs [103].

6.4. Polyphenols and cancer: microRNA interaction

Aging as the most significant risk increases the rate of cancers in human and is an etiologic agent of some cancers like prostate cancer [104]. The continuous effect of male testosterone in normal glandular cells of prostate converts them to adenocarcinoma cells [105]. Zhou et al. has studied the effects of Epigallocatechin-3-gallate on benign prostatic hyperplasia of rats and found that treatment with epigallocatechin-3-gallate has increased the expression of miR-133a/b, which is coupled by angiogenesis decrement, reduced signaling output of growth factors and inhibited Smad3 signaling, which cumulatively caused an inflammation reduction, proliferation and fibrosis of prostate gland [106]. Furthermore, Siddiqui et al. has shown that epigallocatechin-3-gallate reduced the proliferation of prostate cancer cells by blunting the effects of androgenic receptors, resulting a reduced proliferation of prostate cancer cells. Thus, treatment caused a downregulation in miR-21 and an increase in the expression of miR-330, which has proven tumor suppressor qualities [107]. Sakurai et al. has hypothesized that luteolin and gefitinib are able to inhibit the function of Cyclin G-associated kinase (GAK), which is overexpressed in prostatic cancer cell line PC-3, and leads to the increased signaling of epidermal growth factor receptor that cause a higher Gleason score. Also, these two agents partially exerted their effects by increasing the expression of two microRNAs, miR-630 and miR-570, and inhibiting the expression of GAK that increase cell death in prostate cancer cell lines (Table 1) [108].

7. Conclusions and perspectives

Aging is an ever-growing health issue, which affects multiple body systems and many molecules have active roles in the regulation of its process. This study has reviewed that polyphenols are regarded as a therapeutic agent to target numerous pathologies in majority of body systems for long time, say the beneficial effects of Polyphenols in ameliorating and treatment of neurological diseases, cardiovascular diseases, diabetes and many of pathological conditions like inflammation during aging. Alternatively, polyphenols partially exert their effects by modulating the expression and functions of miRNAs that are involved in aging process and covers the expression of large scale of miRNAs that increase insulin secretion or increase insulin sensitivity of body that finally inhibit progression or ameliorate diabetes. Also, oage-related diseases like cardiovascular disease can be affected by miRNAs expressed by Polyphenols and these miRNAs improve heart function by preventing the atherosclerosis or blood pressure. Then, these miRNAs have protective effects against other age-related diseases such as inflammation and cancer by suppression of multiple signaling pathways that produce oxidative stress conditions and this functional juncture has

potential significance in slowing the process of aging. Despite many in vitro and in vivo studies conducted in this regard, no major study has been performed on human subjects that make clinical significance. More clinical studies assessing the relation between polyphenols, aging and miRNAs could enrich our knowledge as a way for detailed studies. Future studies in optimal drug delivery of polyphenols and possible schemes to make clinical use of them will be beneficial.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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