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Compounds that extend longevity are protective in neurodegenerative diseases and provide a novel treatment strategy for these devastating disorders

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ABSTRACT

While aging is the greatest risk factor for the development of neurodegenerative disease, the role of aging in these diseases is poorly understood. In the inherited forms of these diseases, the disease-causing mutation is present from birth but symptoms appear decades later. This indicates that these mutations are well tolerated in younger individuals but not in older adults. Based on this observation, we hypothesized that changes taking place during normal aging make the cells in the brain (and elsewhere) susceptible to the disease-causing mutations. If so, then delaying some of these age-related changes may be beneficial in the treatment of neurodegenerative disease. In this review, we examine the effects of five compounds that have been shown to extend longevity (metformin, rapamycin, resveratrol, N-acetyl-L-cysteine, curcumin) in four of the most common neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis). While not all investigations observe a beneficial effect of these compounds, there are multiple studies that show a protective effect of each of these lifespan-extending compounds in animal models of neurodegenerative disease. Combined with genetic studies, this suggests the possibility that targeting the aging process may be an effective strategy to treat neurodegenerative disease.

1. Introduction

Neurodegenerative diseases are characterized by the progressive dysfunction and degeneration of neurons in the brain and peripheral nervous system. These devastating disorders affect more than 50 million people worldwide. Although genetic and environmental risk factors have been identified for all of these diseases, the pathogenesis of these diseases remains incompletely understood. While symptomatic treatments are available for some of these disorders, there are currently no disease-modifying treatments that can slow disease progression or halt

Abbreviations: 4E-BP, 4E-binding protein; 6−OHDA, 6-hydroxydopamine; AD, Alzheimer's disease; Aβ, Amyloid beta; ALS, amyotrophic lateral sclerosis; AMPK, AMP-activated protein kinase; APP, Amyloid precursor protein; ApoE3, Apolipoprotein E3; ApoE4, Apolipoprotein E4; ATG13, Autophagy Related 13; DLB, Dementia with Lewy bodies; eIF4E, Eukaryotic Translation Initiation Factor 4E; FKBP12, 12 kDa FK506-binding protein; FUS, Fused in sarcoma; GSH, Glutathione; HD, Huntington's disease; HO-1, heme oxygenase-1; Htt, huntingtin; JNK, c-Jun N-terminal kinase; LRRK2, Leucine-Rich Repeat Kinase; MDA, malondialdehyde; MPP+1, methyl-4-phenylpyridinium MPTP1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mTOR, mammalian target of rapamycin; NAC, N-acetyl-L-cysteine; PCG-1α, Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PD, Parkinson's disease; ROS, reactive oxygen species; S6K, Ribosomal protein S6 kinase; SIRT1, sirtuin-1; SN, substantia nigra; SNCA, synuclein alpha; SOD1, Superoxide dismutase 1; T2DM, Type 2 Diabetes Mellitus; TDP-43, TAR DNA-binding protein 43; TOR, target of rapamycin; TORC1, Target of rapamycin complex 1; TORC2, Target of rapamycin complex 2; ULK1, Unc-51 Like Autophagy Activating Kinase 1.

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the loss of neurons. As aging is the greatest risk factor for many of these adult-onset neurodegenerative diseases, including Alzheimer's and Parkinson's disease, it will be important to determine if interventions that extend lifespan can protect against these devastating disorders.

1.1. Alzheimer's disease (AD)

AD is the most common neurodegenerative disorder. AD and other dementias affect 40–50 million people worldwide (Nichols et al., 2019). While there are rare cases of early-onset familial AD affecting individuals under 65 years of age, AD typically affects individuals over 65 years of age, and over 95 % of AD cases are sporadic cases. Moreover, the risk of AD doubles every 5 years after the age of 65. AD is characterized by difficulties with memory, language, problem-solving, and cognitive functions. Brains of AD patients are marked by amyloid plaques, which contain amyloid beta (Aβ), and neurofibrillary tangles, which contain hyperphosphorylated tau. Degeneration starts in the medial temporal lobe, spreads to the hippocampus and amygdala, and eventually to other parts of the brain (Lehéricy et al., 1994; Scahill et al., 2002). Decades of research point towards Aβ aggregation as an important contributor to AD pathogenesis. This could be due to either increased production of Aβ or decreased clearance of Aβ. Aβ oligomers are toxic in neuronal culture (Lambert et al., 1998), contribute to memory deficits in mice (Lesne et al., 2006), and correlate with neurodegeneration in AD patients (McLean et al., 1999). However, therapies targeting Aβ have so far failed in clinical trials, shifting the field towards studying other contributing factors to AD pathogenesis, such as microbial infection (Fulop et al., 2018), dysfunctional vasculature (Zlokovic, 2011), and environmental pollution (Peters et al., 2019). Currently, AD treatments can treat the symptoms but fail to slow disease progression or cognitive decline.

1.2. Parkinson's disease (PD)

PD is the second most common neurodegenerative disease, affecting as many as 10 million individuals worldwide. PD is a movement disorder, which is characterized by the degeneration of dopaminergic neurons within the substantia nigra (SN) and the formation of aggregates, called Lewy bodies, which are primarily composed of a protein called α-synuclein. While interventions are available to control the motor symptoms of PD, there are currently no treatments that can prevent the loss of dopamine neurons or halt the progression of this disease. A growing number of genes have been shown to contribute to the development of PD including *SNCA*, the gene that encodes α-synuclein (Polymeropoulos et al., 1997; Singleton et al., 2003), and *LRRK2,* which encodes a Leucine-Rich Repeat Kinase (Paisan-Ruiz et al., 2004; Zimprich et al., 2004). Nonetheless, the majority of PD cases are considered to be sporadic, as only ~10 % of patients have a direct genetic cause. Although the pathogenesis of PD is incompletely understood, aging is the greatest risk factor for the development of PD (Collier et al., 2011; Driver et al., 2009). Individuals typically do not develop PD until they are 50 years and older. The prevalence of PD is 0.3 % in the general population but increases to 1 % for those over 60 years, and 4 % for those more than 80 years of age. A role for aging in PD is also suggested by the fact that there are many commonalities between PD and normal aging (Rodriguez et al., 2015) including protein aggregation (Tan et al., 2009), increased oxidative stress (Zhou et al., 2008), decreased mitochondrial function (Henchcliffe and Beal, 2008), dysfunction of the proteasome (Cook and Petrucelli, 2009), and impairment of autophagy (Pan et al., 2008).

1.3. Huntington's disease (HD)

HD is the most common inherited neurodegenerative disorder, affecting approximately one in 10,000 individuals. Unlike more widespread disorders, such as AD and PD, HD is entirely due to a single genetic cause: a trinucleotide CAG repeat expansion in the huntingtin (*HTT*) gene. HD is an autosomal dominant disorder which causes motor dysfunction, cognitive deficits, and neuropsychiatric abnormalities. In the brain, HD is characterized by selective degeneration of the striatum and the cortex as well as the appearance of mutant Htt aggregates. Following the discovery of the *HTT* gene, a number of genetic animal models of HD have been generated to study disease mechanisms and treatment (Brignull et al., 2006; Faber et al., 1999; Fernandez-Funez et al., 2000; Gray et al., 2008; Mangiarini et al., 1996; Marsh et al., 2000; Parker et al., 2001; Satyal et al., 2000; Schilling et al., 1999; Slow et al., 2003). Nonetheless, the pathogenesis of HD is not completely understood, and there are currently no approved disease-modifying therapies. An important unanswered question is why HD takes decades to develop when the disease-causing mutation is present in all cells throughout life. The average age of onset for HD is 40 years of age, progressing inevitably to death 10–15 years thereafter. A role for aging in the pathogenesis of HD is supported by the fact that multiple functions that decline with age have also been implicated in the disease including decreased proteasome activity, decreased autophagy, decreased chaperone function, mitochondrial dysfunction, increased oxidative stress, and increased protein aggregation (Bence et al., 2001; Browne and Beal, 2006; DiFiglia et al., 1997; Kitamura et al., 2006; Panov et al., 2002; Ravikumar et al., 2004).

1.4. Amyotrophic lateral sclerosis (ALS)

ALS is the most common adult-onset motor neuron disease, affecting one in 50,000 people in Western countries (Chiò et al., 2013). ALS is caused by degeneration of upper and lower motor neurons, leading to loss of voluntary movement. The disease progresses swiftly, with patients succumbing to the disease within an average of three years after diagnosis (del Aguila et al., 2003). Roughly 95 % of ALS cases are sporadic (Byrne et al., 2011), with the largest known risk factor for sporadic ALS being aging. Both sporadic and familial ALS-onset typically occurs between 40–70 years of age (Alonso et al., 2009). The cellular pathogenesis of ALS is unclear, but a cellular hallmark of ALS is cytoplasmic aggregates in the motor neurons of patients. Over 97 % of sporadic ALS cases have aggregates containing the RNA/DNA binding proteins TAR DNA-binding protein 43 (TDP-43) or fused in sarcoma (FUS) (Deng et al., 2010; Neumann et al., 2006). Mutations in FUS or the TDP-43-encoding gene, transactive response DNA binding protein (TARDBP), can cause familial ALS (Guerrero et al., 2016), and have been used to generate animal models of the disease. Animal models of ALS have also been generated using aggregation-inducing mutations in superoxidase dismutase 1 (SOD1), as this is a common genetic cause of ALS in humans. However, SOD1 animal models and patients do not exhibit FUS aggregation, making it unclear if SOD1 ALS animals are an accurate model for sporadic ALS (Deng et al., 2010). Work with these ALS models and others have identified defects in RNA regulation, phase-separation, nucleocytoplasmic trafficking, stress granule regulation, selective autophagy, and cytoskeleton dynamics (Kim and Taylor, 2017; Taylor et al., 2016; Van Damme et al., 2017). It is unclear if one of these pathways is the driving cause of ALS or if they each contribute to ALS pathogenesis.

1.5. Targeting aging pathways as a therapeutic strategy for neurodegenerative disease

While aging was traditionally considered to be a stochastic process of damage accumulation, it is now clear that lifespan is strongly influenced by genetics. Mutations in a single gene out of many thousand genes can increase lifespan in various model organisms including yeast, flies, worms, and mice, and are associated with longevity in humans. Importantly, genes and interventions that increase lifespan in one species have been shown to be conserved across species (Friedman and Johnson, 1988; Holzenberger et al., 2003; Kenyon et al., 1993; Suh et al., 2008). Interestingly, these lifespan-extending genes have also been shown to be protective in animal models of neurodegenerative disease

including AD (Cohen et al., 2006, 2009; Freude et al., 2009; Killick et al., 2009), PD (Cooper et al., 2015; Knight et al., 2014), HD (Hsu et al., 2003; Jiang et al., 2012; Morley et al., 2002; Sadagurski et al., 2011), and ALS (Boccitto et al., 2012). This strongly suggests that targeting molecular pathways that modulate aging may be an effective strategy to treat neurodegenerative disease. Despite these exciting observations, it remains a challenge to translate genetic treatments to humans.

As an alternative, it may be possible to develop novel treatments for neurodegenerative diseases using compounds that modulate aging. In addition to identifying a plethora of genes that can affect longevity (https://genomics.senescence.info/genes/), aging research has also identified multiple compounds that extend lifespan in model organisms (http://genomics.senescence.info/drugs/). In this review, we examine the effects of five compounds that have been shown to modulate aging (metformin, resveratrol, rapamycin, N-acetyl-L-cysteine, and curcumin) in four neurodegenerative diseases (AD, PD, HD and ALS). We find that compounds that increase lifespan can be neuroprotective in models of neurodegenerative disease (Fig. 1), and thus may represent a novel treatment strategy for these disorders.

2. Metformin

Metformin is a promising preventative treatment for age-associated diseases. Metformin is commonly used for treating Type 2 Diabetes Mellitus (T2DM), and retrospective studies discovered that metformin treatment of T2DM patients caused reduced incidents of age-associated diseases such as cardiovascular diseases (Campbell et al., 2017), cancers (Gandini et al., 2014; Wu et al., 2014), and neurodegenerative diseases (Cheng et al., 2014; Ng et al., 2014). In T2DM patients, metformin causes reduced glucose production in the liver, as well as increased insulin sensitivity in the peripheral tissues (Giannarelli et al., 2003). Metformin is delivered orally and disperses throughout the body to the liver, kidney, muscles, and the brain (Gormsen et al., 2016; Kulkarni et al., 2018; Labuzek et al., 2010), which may explain its widespread physiological effects. The specific molecular interactions of metformin are still unclear. However, metformin leads to activation of the highly conserved energy-sensing AMP-activated protein kinase (AMPK) pathway (Fullerton et al., 2013; Zhou et al., 2001). Metformin also independently activates mTORC1, which causes activation of AMPK through a lysosomal pathway (Kalender et al., 2010; Zhang et al., 2016). Activation of the AMPK pathway corrects energy imbalances by increasing lipid metabolism, increasing mitochondrial biogenesis, increasing autophagy, delaying cell cycle progression, and decreasing protein production (Hardie et al., 2012). The AMPK pathway also modulates inflammation and inhibits the c-Jun N-terminal kinase (JNK) pathway (Chen et al., 2019; Hu et al., 2016). Therefore, metformin treatment regulates multiple pathways associated with aging.

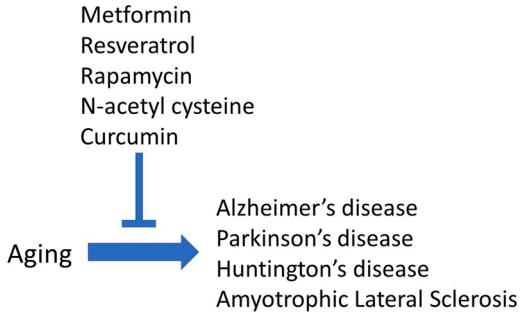

Fig. 1. Lifespan-extending compounds can be protective in neurodegenerative diseases. Five compounds that have been shown to increase lifespan in model organisms (metformin, resveratrol, rapamycin, N-acetyl cysteine, curcumin) have all been shown to have beneficial effects in four different neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis).

2.1. Effect of metformin on lifespan

Metformin has mixed effects on lifespan in various model organisms (Table 1), but improves healthspan experimentally in murine models and is associated with decreases in age-related diseases in humans with T2DM. Metformin was first shown to extend lifespan in *C. elegans* (Onken and Driscoll, 2010), but, interestingly, this effect was due to metabolic changes in the bacterial food source, not the nematodes (Cabreiro et al., 2013). Subsequent studies were unable to demonstrate a beneficial effect of metformin on lifespan in Drosophila (Slack et al., 2012). In mice, metformin was shown to cause a small, but statistically significant, increase in lifespan (Martin-Montalvo et al., 2013). However, a larger study performed at multiple locations with genetically heterogenous mice failed to find a statistically significant increase in lifespan when animals were treated with metformin alone (Strong et al., 2016). Nonetheless, metformin exhibits a more clearly beneficial effect on the healthspan of mice (Feng et al., 2020; Martin-Montalvo et al., 2013). This is consistent with previous research showing that metformin improves cardiovascular function and cognition in aging mice (Campbell et al., 2017; UKPDS, 1998). In retrospective cohort studies, metformin was associated with extended lifespan of T2DM patients (Bannister et al., 2014; Campbell et al., 2017). Based on these promising results, a large randomized controlled study has been planned to determine if metformin affects lifespan and healthspan in healthy humans (Barzilai et al., 2016).

Table 1
Effect of compounds on lifespan in model organisms.

Compound	Mechanisms	*C. elegans*	Drosophila	Mouse
Metformin	Activates AMPK Activates mTORC1	Increase[1]	No effect[2]	Increase[3] No effect[4]
Resveratrol	Activates SIRT1 Activates AMPK Antioxidant Anti-inflammatory	Increase[5–8]	Increase[5, 9]	No effect[10] Increase[11] (mice on high fat diet)
Rapamycin	mTORC1 inhibition	Increase[12]	Increase[13]	Increase[14–18]
NAC	Antioxidant	Increase[19]	Increase[20]	Increase[21] (possibly through dietary restriction)
Curcumin	Antioxidant Anti-inflammatory	Increase[22]	Increase[23–26]	Increase[27] No effect[28]

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2.2. Metformin and Alzheimer's disease

In the majority of studies reported, metformin is protective against dementia and AD in model organisms and in humans (Table 2). Treatment with metformin ameliorates phenotypic deficits in AD models in cell culture (Chen et al., 2016), *C. elegans* (Ahmad and Ebert, 2017), Drosophila (Niccoli et al., 2016), and mice (Chen et al., 2019; Farr et al., 2019; Ou et al., 2018). Metformin treatment after phenotypic onset improved behavioral phenotypes in APP/PS1 mice (Matthes et al., 2018) and in an STZ-induced AD rodent model (Nassar et al., 2018). In contrast, metformin treatment exacerbated motor and behavioral deficits in a P301S mutant human tau mouse model (Barini et al., 2016). Metformin treatment also increased tau phosphorylation in murine AD models expressing human ApoE3 or ApoE4 (Zhang et al., 2019). Interestingly, metformin still improved cognition in the ApoE3 mouse, but not the ApoE4 mice, suggesting that genetic differences can influence the efficacy of metformin in treating AD. Another cautionary note is that metformin can cause increased Aβ production, which is inhibited by insulin (Chen et al., 2009). In patients with T2DM, metformin treatment alone was associated with a decrease in the risk of dementia in multiple retrospective cohort studies (Bohlken et al., 2018; Cheng et al., 2014; Hsu et al., 2011; Orkaby et al., 2017; Shi et al., 2019). However, two studies did find that metformin treatment of T2DM patients was associated with an increased risk of developing AD (Imfeld et al., 2012; Kuan et al., 2017). Metformin has been proposed to be protective against AD by inhibiting the JNK pathway, causing suppression of cell death (Chen et al., 2016). It may also be protective through increasing glucose transport in neurons (Niccoli et al., 2016). While metformin has promising effects on AD models, more research needs to be done to determine why it has detrimental effects in certain systems.

2.3. Metformin and Parkinson's disease

Metformin may reduce the risk of developing PD (Table 3). Of three retrospective cohort studies, two found that metformin-treated T2DM patients had reduced risk of developing PD (Shi et al., 2019; Wahlqvist et al., 2012), while the other found an increased risk of developing PD (Kuan et al., 2017). Experimentally, metformin is protective in PD models in cell culture (Dulovic et al., 2014; Kang et al., 2017), *C. elegans* (Saewanee et al., 2019), Drosophila (Ng et al., 2012), and in mice (Kang et al., 2017; Lu et al., 2016). Metformin appears to be protective against PD through the activation of AMPK, though dopaminergic neurons do not need to have functioning AMPK for metformin to be protective (Bayliss et al., 2016). Several downstream targets of AMPK have been identified as possibly delaying PD symptoms, specifically inhibiting microglia overactivation (Lu et al., 2016) and activation of the PGC-1α pathway, which stimulates mitochondrial biogenesis (Kang et al., 2017). Interestingly, while metformin increases autophagy induction (Lu et al., 2016), autophagy is not required for the protective effects of metformin (Dulovic et al., 2014).

2.4. Metformin and Huntington's disease

Metformin consistently suppresses or delays HD phenotypic deficits in cell culture (Jin et al., 2016), *C. elegans* (Sanchis et al., 2019; Vázquez-Manrique et al., 2016), mice (Arnoux et al., 2018; Sanchis et al., 2019), and humans (Hervás et al., 2017) (Table 4). Most promisingly, diabetic HD patients treated with metformin exhibited improved cognitive functions compared to nondiabetic HD controls (Hervás et al., 2017). This delay of HD symptoms may be due to decreased translation of mutant HTT, the protein which drives HD disease progression (Arnoux et al., 2018; Sanchis et al., 2019). The protective effect of metformin may also be due to its ability to prevent mitochondrial depolarization as shown in mHTT striatal cell culture (Jin et al., 2016).

2.5. Metformin and amyotrophic lateral sclerosis

Based on the limited number of studies that have been reported, metformin has either negligible or exacerbating effects on ALS (Table 5). In the single experimental study identified, metformin treatment of SOD1(G93A) male mice caused no effect, while treatment of SOD1 (G93A) female mice caused a decreased age of onset and increased rate of disease progression (Kaneb et al., 2011). A retrospective cohort study determined that metformin treatment had no effect on the progression of

Table 2
Effect of compounds on Alzheimer's disease.

Compound	Cell Culture	*C. elegans*	Drosophila	Mouse	Human
Metformin	Protective[1, 2]	Protective[3]	Protective[4]	Protective[5–10] Deleterious[11]	Protective[12–16] Deleterious[17, 18]
Resveratrol	Protective[19–24]	Protective[25]	N/A	Protective[26–32]	Protective[33, 34] No effect[35]
Rapamycin	Deleterious[36, 37]	N/A	Protective[38, 39]	Protective[40–43] Deleterious[44]	N/A
NAC	Protective[45]	N/A	N/A	Protective[46, 47]	Protective[48]
Curcumin	Protective[49, 50]	Protective[51]	Protective[52]	Protective[53–55]	N/A

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Table 3
Effect of compounds on Parkinson's disease.

Compound	Cell Culture	*C. elegans*	Drosophila	Mouse	Human
Metformin	Protective[1–4]	Protective[5]	Protective[6]	Protective[1, 2, 4, 7, 8]	Protective[9, 10] Deleterious[11]
Resveratrol	Protective[12–15]	N/A	Deleterious[16]	Protective[15, 17–23]	N/A
Rapamycin	Protective[24, 25]	Protective[26]	Protective[27]	Protective[24, 25, 28, 29]	N/A
NAC	Protective[30]	N/A	N/A	Protective[31, 32]	Protective[30]
Curcumin	Protective[33–36]	N/A	Protective[37]	Protective[38–45]	N/A

1. Lu M, et al. (2016) Int *J* Neuropsychopharmacol 19(9). 2. Bayliss JA, et al. (2016) PloS one 11(7). 3. Dulovic M, et al. (2014) Neurobiology of disease 63. 4. Kang H, et al. (2017) Oncotarget 8(30). 5. Saewanee N, et al. (2019) Neuroscience Research. 6. Ng C-H, et al. (2012) *J* Neurosci 32(41). 7. Adedeji HA, et al. (2014) Prog Neuropsychopharmacol Biol Psychiatry 48. 8. Yan Q, et al. (2017) Mol Pharmacol 92(6). 9. Wahlqvist ML, et al. (2012) Parkinsonism Relat Disord 18(6). 10. Shi Q, et al. (2019) BMJ Open 9(7). 11. Kuan Y-C, et al. (2017) Prog Neuropsychopharmacol Biol Psychiatry 79(Pt B). 12. Alvira D, et al. (2007) Neuroscience 147(3). 13. Wu Y, et al. (2011) Neuro-Signals 19(3). 14. Ferretta A, et al. (2014) Biochimica et biophysica acta 1842(7). 15. Wang ZH, et al. (2015) Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 74. 16. Bagatini PB, et al. (2011) Invertebrate neuroscience : IN 11(1). 17. Blanchet J, et al. (2008) Progress in neuro-psychopharmacology & biological psychiatry 32(5). 18. Jin F, et al. (2008) European journal of pharmacology 600(1–3). 19. Khan MM, et al. (2010) Brain research 1328. 20. Gaballah HH, et al. (2016) Chemico-biological interactions 251. 21. Zhang LF, et al. (2018) Food & function 9(12). 22. Liu Q, et al. (2019) Behavioural brain research 367. 23. Xia D, et al. (2019) Journal of cellular biochemistry 120(4). 24. Malagelada C, et al. (2010) J Neurosci 30(3). 25. Dehay B, et al. (2010) J Neurosci 30(37). 26. Tyson T, et al. (2017) Sci Rep 7(1). 27. Tain LS, et al. (2009) Nat Neurosci 12(9). 28. Masini D, et al. (2018) Front Neurol 9. 29. Crews L, et al. (2010) PLoS One 5(2). 30. Monti DA, et al. (2016) PLoS One 11(6). 31. Rahimmi A, et al. (2015) Brain Research Bulletin 113. 32. Clark J, et al. (2010) PloS one 5 (8). 33. van der Merwe C, et al. (2017) Mol Neurobiol 54(4). 34. Jayaraj RL, et al. (2013) J Mol Neurosci 51(3). 35. Qualls Z, et al. (2014) Neurotox Res 25(1). 36. Sang Q, et al. (2018) Cell Physiol Biochem 51(2). 37. Nguyen TT, et al. (2018) Oxid Med Cell Longev 2018. 38. Zbarsky V, et al. (2005) Free Radic Res 39(10). 39. Du XX, et al. (2012) Neurosci Bull 28(3). 40. Rajeswari A, et al. (2008) Inflammopharmacology 16(2). 41. Chiu S, et al. (2013) J Complement Integr Med 10. 42. Pan J, et al. (2012) Translational Neurodegeneration 1. 43. Jayaraj RL, et al. (2014) Biomed Res Int 2014. 44. Abbaoui A, et al. (2017) Neurosci Lett 660. 45. Sharma N, et al. (2018) Inflammopharmacology 26(2).

Table 4
Effect of compounds on Huntington's disease.

Compound	Cell Culture	*C. elegans*	Drosophila	Mouse	Human
Metformin	Protective[1]	Protective[2, 3]	N/A	Protective[2, 4, 5]	Protective[6]
Resveratrol	Protective[7, 8]	Protective[7]	Protective[9, 10]	Protective[8, 11, 12]	N/A
Rapamycin	Protective[13, 14]	N/A	Protective[15]	Protective[15] No effect[16]	N/A
NAC	N/A	N/A	N/A	Protective[17, 18]	N/A
Curcumin	N/A	N/A	Protective[19]	Protective[20]	N/A

1. Jin J, et al. (2016) Neuromolecular Med 18(4). 2. Sanchis A, et al. (2019) Exp Mol Med 51(6). 3. Vázquez-Manrique RP, et al. (2016) Hum Mol Genet 25(6). 4. Arnoux I, et al. (2018) Elife 7. 5. Ma TC, et al. (2007) Neurosci Lett 411(2). 6. Hervás D, et al. (2017) PloS one 12(6). 7. Parker JA, et al. (2005) Nature genetics 37(4). 8. Naia L, et al. (2017) Molecular neurobiology 54(7). 9. Pallos J, et al. (2008) Human molecular genetics 17(23). 10. Maher P, et al. (2011) Human molecular genetics 20 (2). 11. Ho DJ, et al. (2010) Experimental neurology 225(1). 12. Gerhardt E, et al. (2011) PloS one 6(12). 13. Ravikumar BD, R.; Rubinsztein, C. (2002) Hum Mol Genet 11. 14. King MA, et al. (2008) Mol Pharmacol 73(4). 15. Ravikumar B, et al. (2004) Nat Genet 36(6). 16. Fox JH, et al. (2010) Mol Neurodegener 5. 17. Sandhir R, et al. (2012) Neurodegenerative Diseases 9(3). 18. Wright DJ, et al. (2015) Translational Psychiatry 5(1). 19. Chongtham A, et al. (2016) Sci Rep 6. 20. Hickey MA, et al. (2012) Mol Neurodegener 7.

Table 5
Effect of compounds on amyotrophic lateral sclerosis.

ALS	Cell Culture	*C. elegans*	Drosophila	Mouse	Human
Metformin	N/A	N/A	N/A	Deleterious[1]	No effect[2]
Resveratrol	Protective[3]	N/A	N/A	Protective[4]	N/A
Rapamycin	Protective[5]	N/A	Protective[6]	Protective[7] No effect[8] Deleterious[9]	In Progress[10]
NAC	Protective[11]	N/A	N/A	Protective[12]	Deleterious[13]
Curcumin	Protective[14, 15]	N/A	N/A	N/A	Protective[16, 17]

1. Kaneb et al., 2011 PloS one 6(9). 2. Bond L, et al. (2020) Behavioral Sciences 10(1). 3. Kim D, et al. (2007) The EMBO journal 26(13). 4. Mancuso R, et al. (2014) Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics 11(2). 5. Caccamo A, et al. (2009) J Biol Chem 284(40). 6. Cheng CW, et al. (2015) J Neurogenet 29(2-3). 7. Wang IF, et al. (2012) Proc Natl Acad Sci U S A 109(37). 8. Staats et al., 2013 Mol Neurodegener 8. 9. Zhang X, et al. (2011) Autophagy 7(4). 10. Mandrioli J, et al. (2018) Medicine (Baltimore) 97(24). 11. Beretta S, et al. (2003) Neurobiology of disease 13(3). 12. Andreassen OA, et al. (2000) Neuroreport 11(11). 13. Deepmala, et al. (2015) Neuroscience & Biobehavioral Reviews 55. 14. Lu J, et al. (2012) Brain Res Bull 89(5–6). 15. Dong H, et al. (2014) Neuroscience 272. 16. Ahmadi M, et al. (2018) Neurotherapeutics 15(2). 17. Chico L, et al. (2018) CNS Neurol Disord Drug Targets 17(10).

ALS in T2DM patients (Bond et al., 2020).

3. Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is a polyphenol found in purple grapes, red wine and many plants. Its potential benefits were first manifested through the "French Paradox", which associated red wine consumption with decreased risk of cardiovascular diseases (Renaud and de Lorgeril, 1992). Although red wine content in resveratrol is insufficient to provide significant pharmacological effects (Vitaglione et al., 2005; Walle et al., 2004), resveratrol has been associated with many benefits such as anti-carcinogenic (Jang and Pezzuto, 1999), cardioprotective (Ungvari et al., 2007), and neuroprotective effects (Bastianetto et al., 2015). The mechanism underlying its protection is

not completely understood. The conserved NAD-dependent deacetylase sirtuin-1, SIRT1, and its invertebrate homologue SIR-2 were initially believed to mediate the lifespan-extending effect and protection conferred by resveratrol (Howitz et al., 2003; Viswanathan et al., 2005; Wood et al., 2004). However, these findings have been debated considering that sirtuin-independent lifespan extension was observed (Bass et al., 2007; Zhang, 2006) and that resveratrol did not directly affect SIRT1 activity (Beher et al., 2009; Kaeberlein et al., 2005; Pacholec et al., 2010). Furthermore, resveratrol activates AMP-activated kinase (AMPK) in both SIRT-1 dependent and independent manner (Dasgupta and Milbrandt, 2007; Price et al., 2012; Suchankova et al., 2009). Whether SIRT-1 is involved in the protective effects of resveratrol is yet to be confirmed. Other reported activities of resveratrol include reducing oxidative damage by acting as an anti-oxidant (Li et al., 2014a), reducing neuroinflammation through inhibition of the NFκB pro-inflammatory pathway (Das and Das, 2007; Manna et al., 2000; Zhang et al., 2010b), decreasing neuronal apoptosis via acetylation of p53 pro-apoptotic factor (Kim et al., 2007; Luo et al., 2001; Vaziri et al., 2001), and improving mitochondrial functions through PGC-1α activation (Naia et al., 2017; Price et al., 2012).

3.1. Effect of resveratrol on lifespan

Resveratrol was first observed to extend lifespan in yeast (Howitz et al., 2003) and the same effect was later demonstrated in *C. elegans* (Bass et al., 2007; Gruber et al., 2007; Viswanathan et al., 2005; Wood et al., 2004), Drosophila (Bauer et al., 2004; Wood et al., 2004), and honey bees (Rascón et al., 2012) (Table 1). Lifespan extension by resveratrol in vertebrates was only observed in the fish *N. furzeri* (Valenzano et al., 2006), as resveratrol failed to extend lifespan in mice (Strong et al., 2013), except in mice that were placed on a high calorie diet (Baur et al., 2006). However, evidence from rodent studies suggest that resveratrol can increase neuronal cell viability (Albani et al., 2009) and delay onset of age-related diseases (Pearson et al., 2008). The mechanism underlying the lifespan-extending effect of resveratrol is mainly unknown, although some studies showed that this relies on AMPK activation and related changes in metabolism (Apfeld et al., 2004; Greer et al., 2007). While resveratrol increased lifespan in simple animal models, additional research will be required to determine why this effect was not observed in mammals.

3.2. Resveratrol and Alzheimer's disease

Resveratrol improves AD pathology in many studies (Table 2), but its mechanisms of action are unclear. Both rodent and cell line models of AD treated with resveratrol showed decreased amyloid-β aggregation and reduced cytotoxicity (Capiralla et al., 2012; Huang et al., 2011; Karuppagounder et al., 2009; Marambaud et al., 2005; Porquet et al., 2013; Vingtdeux et al., 2010; Zhao et al., 2015). The same effect was also observed in *C. elegans* (Regitz et al., 2016). Moreover, tau hyperphosphorylation was found to be reduced by resveratrol treatment (Lin et al., 2018; Porquet et al., 2013; Schweiger et al., 2017), along with reduced levels of oxidative damage (Granzotto and Zatta, 2011; Huang et al., 2011; Lin et al., 2018). These effects appear to be mediated by an increased production of antioxidants such as heme oxygenase-1 (HO-1) and glutathione (GSH) through the Nrf2 pathway (Chen et al., 2005; Huang et al., 2011; Kong et al., 2019; Sharma and Gupta, 2002). Additionally, SIRT1 activation is believed to mediate many of the beneficial effects of resveratrol on AD impairments (Cristòfol et al., 2012; Porquet et al., 2013) and might act through reducing neuronal apoptosis (Feng et al., 2013; Kim et al., 2007). Resveratrol can also promote Aβ clearance through the AMPK pathway (Porquet et al., 2013; Vingtdeux et al., 2010). Furthermore, resveratrol treatment decreased neuroinflammation in rodent models (Capiralla et al., 2012; Gong et al., 2010), as well as in a recent clinical trial conducted on AD patients (Moussa et al., 2017). However, other human studies have shown mixed results (Moussa et al., 2017; Turner et al., 2015; Zhu et al., 2018). Together, these findings show a protective effect of resveratrol in AD models, while further human clinical trials will be necessary to determine the efficacy of resveratrol for AD treatment.

3.3. Resveratrol and Parkinson's disease

Resveratrol improves PD-associated impairments in various PD rodent models (Table 3), including the 6−OHDA rat model (Jin et al., 2008; Khan et al., 2010) and the MPTP-treated mouse model (Blanchet et al., 2008; Liu et al., 2019; Wang et al., 2015; Xia et al., 2019). A decrease in α-synuclein aggregation, dopamine loss and oxidative stress was observed after resveratrol treatment (Gaballah et al., 2016; Khan et al., 2010; Zhang et al., 2018), along with reduced neuroinflammation (Jin et al., 2008; Liu et al., 2019; Lofrumento et al., 2014). The specific mechanism by which resveratrol exerts its effects in PD is still unknown. However, resveratrol was shown to act through enhanced autophagy (Ferretta et al., 2014; Wu et al., 2011), decreased apoptosis (Alvira et al., 2007; Xia et al., 2019), and mitochondrial biogenesis (Ferretta et al., 2014). These improvements require AMPK and SIRT1 activation (Ferretta et al., 2014; Wu et al., 2011), as well as the SIRT1 target PGC-1α (Ferretta et al., 2014). Combined, these studies demonstrate a potential protective role of resveratrol in PD.

3.4. Resveratrol and Huntington's disease

HD-associated phenotypes such as neuronal degeneration were reduced by resveratrol treatment in many HD animal models, including *C. elegans* (Parker et al., 2005), Drosophila (Maher et al., 2011; Pallos et al., 2008) and multiple rodent models (Ho et al., 2010; Naia et al., 2017) (Table 4). Similar to PD models, resveratrol treatment in HD models is believed to act through SIRT1 to increase neuronal viability (Ho et al., 2010; Naia et al., 2017; Parker et al., 2005). Furthermore, SIRT1 activation by resveratrol may increase PGC-1α expression (Ho et al., 2010; Naia et al., 2017). PGC-1α is involved in mitochondrial biogenesis and functions, and its reduced expression may contribute to the mitochondrial defects in HD (Naia et al., 2017). Therefore, PGC-1α might mediate some of the protective effects of resveratrol in HD models.

3.5. Resveratrol and amyotrophic lateral sclerosis

Research on the effects of resveratrol in ALS is scarce. A first report in ALS cell lines and SOD1 mouse models showed increased neuronal survival and decreased neurodegeneration after treatment with resveratrol (Kim et al., 2007; Mancuso et al., 2014). Additionally, activation of SIRT1 and reduced acetylation of p53 were observed (Kim et al., 2007; Mancuso et al., 2014), as well as the activation of AMPK (Mancuso et al., 2014). These findings indicate that resveratrol may be protective in ALS (Table 5), through the same mechanisms that are proposed to contribute to protection in other neurodegenerative diseases.

4. Rapamycin

Rapamycin, also known as sirolimus, is an inhibitor of the evolutionarily conserved target of rapamycin (TOR). It is an anti-fungal metabolite produced by *Streptomyces hygroscopicus* (Li et al., 2014b). Rapamycin inhibits TOR activity by acting as a "lynchpin" in a molecular interaction between TOR and FKBP12 that impedes TOR from phosphorylating its downstream targets (Choi et al., 1996; Stan et al., 1994; Stanfel et al., 2009). TOR is active in target of rapamycin complex 1 and 2 (TORC1 and TORC2), which together act as key regulators of cellular metabolism and growth (Stanfel et al., 2009). It is thought that the benefits of short-term doses of rapamycin are due to TORC1 inhibition (Stanfel et al., 2009), resulting in several changes including inhibition of protein synthesis and stimulation of autophagy (Kapahi et al.,

2010; Stanfel et al., 2009).

4.1. Effect of rapamycin on lifespan

Rapamycin treatment increases lifespan in *C. elegans* (Robida-Stubbs et al., 2012), Drosophila (Bjedov et al., 2010), and mice (Fok et al., 2014; Harrison et al., 2009; Miller et al., 2011; Wilkinson et al., 2012; Zhang et al., 2014) (Table 1). Interestingly, rapamycin has also been reported to increase immune function in older humans and it has been suggested that it could be used to ameliorate immunosenescence in the elderly population (Mannick et al., 2014; Mannick et al., 2018). Increased mTOR activity has been implicated in multiple hallmarks of aging, including deregulated protein synthesis and decreased autophagy (Johnson et al., 2013; Kapahi et al., 2010; Laplante and Sabatini, 2012). One way in which rapamycin is thought to slow aging is by reducing protein synthesis via TORC1 inhibition (Lamming et al., 2013). Inhibition or loss of the TORC1 effector, ribosomal S6 kinase (S6K), has been shown to enhance longevity by reducing translation initiation in model organisms (Hansen et al., 2007; Kapahi et al., 2004; Pan et al., 2007; Selman et al., 2009). Furthermore, studies in *C. elegans* show that inhibition of the cap-dependent eukaryotic translation initiation factor 4E (eIF4E) plays a significant role in increasing lifespan through TORC1 inhibition (Hansen et al., 2007; Pan et al., 2007; Syntichaki et al., 2007). Rapamycin treatment may therefore reduce cap-dependent translation, thereby increasing cap-independent translation, which may allow for expression of stress-response genes (Bjedov et al., 2010). Rapamycin is also thought to slow aging by stimulating autophagy (Lamming et al., 2013). TORC1 inhibition results in increased levels of AMPK-activated ULK1 and ATG13 (Laplante and Sabatini, 2009), which, together, initiate autophagosome formation and allow for clearance of accumulated material in the cell (Ganley et al., 2009; Kim et al., 2011).

4.2. Rapamycin and Alzheimer's disease

Activation of the downstream effectors of TOR is increased in AD models, suggesting that over-active TORC1 could be contributing to pathology in AD brains (An et al., 2003; Griffin et al., 2005; Li et al., 2004; Pei et al., 2006). In Drosophila AD models, rapamycin treatment results in decreased levels of tau toxicity, apoptotic neurons, neurodegenerative markers, and increased survival (Berger et al., 2006; Khurana et al., 2006). Studies in both PDAPP and 3xTg-AD mouse models have also reported reduced Aβ and tau toxicity as well as amelioration of cognitive deficits in response to rapamycin treatment (Caccamo et al., 2010; Majumder et al., 2011; Spilman et al., 2010). Additionally, in hAPP(J20) mice, rapamycin protected the blood brain barrier, which is often critically disrupted in AD (Van Skike et al., 2018). However, studies with cells expressing human APP and studies with Tg2576 mice suggest that inhibition of mTORC1 by rapamycin can also exacerbates Aβ toxicity (Yu et al., 2005; Zhang et al., 2010c). Together, these findings suggest that rapamycin may be able to attenuate AD phenotypes (Table 2), but further studies are required to determine why, in certain AD models, rapamycin may augment Aβ toxicity.

4.3. Rapamycin and Parkinson's disease

Both increased mTOR activity and reduced autophagy are seen in mouse PD models and in patients with dementia with Lewy bodies (DLB) (Crews et al., 2010). The effects of rapamycin in PD models have largely been linked to reduced translation initiation via S6K and eIF4E as well as recovery of autophagy levels, both mediated by TORC1 inhibition (Bove et al., 2011). Treatment with rapamycin improves neurodegenerative phenotypes seen in PD models of Drosophila (Table 3), including climbing ability and survival of dopaminergic neurons. It was also shown in Drosophila that 4E-binding protein (4E-BP), a downstream effector of TOR and inhibitor of translation initiation factor eIF4E, is required for rapamycin protection (Tain et al., 2009). Furthermore, rapamycin reduces α-synuclein accumulation in neurons, improves lysosomal function and reduces neurodegeneration in C57BL/6 mice expressing human α-synuclein (D-line tg mice) (Crews et al., 2010). Additionally, in mice and human dopaminergic neuroblastoma cells treated with parkinsonian toxins, rapamycin enhanced autophagy and protected against death of neurons (Dehay et al., 2010; Malagelada et al., 2010). Rapamycin also improved memory deficits and depressive and anxiety-like behaviours in murine models (Masini et al., 2018), illustrating its ability to rescue both molecular and behavioural markers of PD.

4.4. Rapamycin and Huntington's disease

The putative role of mTOR in HD is demonstrated by the observations that overexpression of mutant Htt enhances mTORC1 activity in mouse striatal cells and HEK293 cells, and that enhanced mTORC1 activity in the striatum of HD mice results in premature death and severe motor defects (Pryor et al., 2014). Rapamycin reduces mutant Htt aggregates in Drosophila, in the N171-82Q mouse model, and in mammalian cells expressing exon 1 of the mutant HD gene with disease-length polyglutamine expansion (King et al., 2008; Ravikumar et al., 2004; Ravikumar and Rubinsztein, 2002). Both Drosophila and mouse models of HD also show improved motor function with rapamycin treatment (Ravikumar et al., 2004) (Table 4). Proposed mechanisms of action include both induction of autophagy and reduction of protein synthesis (King et al., 2008; Ravikumar et al., 2004; Ravikumar and Rubinsztein, 2002). However, other studies suggest that while rapamycin may reduce protein synthesis and improve motor function, it may also have no effect on mutant Htt levels and may not be neuroprotective in R6/2 mouse models of HD (Fox et al., 2010). Therefore, while rapamycin acted as a promising therapeutic in many HD models, further studies should be conducted to distinguish between rapamycin's effects on motor function and mutant Htt in mouse models.

4.5. Rapamycin and amyotrophic lateral sclerosis

Rapamycin increases survival and suppresses locomotor deficits in TDP-43 Drosophila models of ALS (Cheng et al., 2015) (Table 5). Similarly, in murine TDP-43 models of ALS, rapamycin treatment also reduced neuronal death, reduced accumulation of abnormal TDP-43 and reduced loss of motor functions (Wang et al., 2012). Studies in TDP-43 cell lines also report that rapamycin reduces abnormal TDP-43 (Caccamo et al., 2009). Notably, in all TDP-43 animal models of ALS, there is strong evidence that the activation of autophagy mediates the therapeutic effects seen with rapamycin treatment (Caccamo et al., 2009; Cheng et al., 2015; Wang et al., 2012). In contrast, in SOD1 murine models of ALS, it has been observed that rapamycin does not reduce neuronal death, nor does it increase survival (Staats et al., 2013; Zhang et al., 2011). It is important to note that SOD1 mouse models do not display TDP-43 aggregation (Turner et al., 2008) and that TDP-43 aggregates are seen in most sporadic ALS cases (Prasad et al., 2019), suggesting that the SOD1 mouse model may not be representative of the pathology seen in the majority of ALS cases (Turner et al., 2008). Rapamycin has been recognized as a promising therapeutic for ALS patients and currently, a clinical trial in Italy is investigating rapamycin and riluzole as a potential combination therapy (Mandrioli et al., 2018).

5. N-acetyl cysteine

N-acetyl-*L*-cysteine (NAC) is a thiol, a mucolytic agent and an antioxidant. Most commonly known as a treatment for acetaminophen toxicity, NAC has a wide range of clinical applications primarily due to its ability to act as an antioxidant (Dekhuijzen, 2004). Despite its widespread use, how NAC acts as an antioxidant is still unclear. While it was originally believed that NAC scavenges oxidants such as hydrogen peroxide (H_2O_2) and superoxide ($O_2^{\cdot-}$) by using its thiol group to reduce

them, it has been suggested that the rate constants of these reactions are too low for this to be likely (Ezerina et al., 2018). Instead, it has been proposed that NAC derives most of its antioxidant properties from being a cysteine precursor, resulting in elevated synthesis of glutathione (GSH), a critical and ubiquitous thiol antioxidant (Arakawa and Ito, 2007). GSH contributes to enzymatic and non-enzymatic antioxidant systems and is thus important for protection against many toxins (Bump and Brown, 1990). NAC also protects cells from apoptosis by activating extracellular signal-related kinase pathways (Zafarullah et al., 2003). Thus, NAC acts as an antioxidant through its capacity as a free radical scavenger and as a cysteine precursor, elevating intracellular concentrations of GSH.

5.1. Effect of N-acetyl cysteine on lifespan

NAC has been shown to increase longevity in various model organisms (Table 1). In *C. elegans,* NAC treatment at 5 mM increases mean lifespan by up to 30.5 % (Oh et al., 2015), while increased concentrations of 10 mM cause a smaller increase of mean lifespan (Yang and Hekimi, 2010). In Drosophila, NAC significantly increases median lifespan by up to 26.6 % at 10 mg/ml concentrations (Brack et al., 1997), while higher concentrations are toxic leading to a significant decrease in lifespan (Niraula and Kim, 2019). The effect of NAC treatment in mice is sex-dependent, as it increases mean lifespan in males but not in females (Flurkey et al., 2010). It is important to note however that mice treated with NAC exhibit reduced food intake which is also shown to increase lifespan in mice (Flurkey et al., 2010). Hence, it is possible that dietary restriction contributes to NAC's effect on lifespan in mice.

5.2. N-acetyl cysteine and Alzheimer's disease

NAC protects against Aβ-induced apoptosis in cultured cortical neurons by stimulating p35/Cdk5-mediated synaptic plasticity (Hsiao et al., 2008) and reducing JNK activity (Xu et al., 2009) (Table 2). NAC may also help protect against the neuro-inflammatory aspect of AD by increasing intracellular concentrations of GSH in glial cells and astrocytes (Tardiolo et al., 2018). In Aβ-injected and streptozotocin-induced rodent AD models, NAC treatment alleviates AD-induced cognitive deficits (Costa et al., 2016; Shahidi et al., 2017) by restoring the cortical and hippocampal cholinergic system and alleviating of oxidative stress (Huang et al., 2010; Prakash et al., 2015; Tchantchou et al., 2005). Clinical trials of NAC as a treatment for AD have yielded insignificant and mixed results (Deepmala Slattery et al., 2015). The largest controlled trial reports favourable changes in almost all cognitive outcome measures when patients were treated with NAC; however, only a few changes were significant (Adair et al., 2001). Additional trials with greater sample sizes would be needed to determine if NAC can act as an AD treatment.

5.3. N-acetyl cysteine and Parkinson's disease

NAC is protective in both animal models of PD, and PD patients (Table 3). PD is associated with decreased GSH concentration in the substantia nigra, potentially due to mitochondrial dysfunction and oxidative stress (Bavarsad Shahripour et al., 2014). NAC treatment significantly increases the survival of iPSC-derived dopaminergic neurons treated with rotenone to model PD (Monti et al., 2016). NAC treatment of rotenone-induced PD murine models protects against motor deficits and loss of dopaminergic neurons (Rahimmi et al., 2015). In murine models, it is thought that protection of dopaminergic neurons is mediated by the antioxidant capacity of NAC. Thus, increasing GSH synthesis may be protecting against α-synuclein toxicity (Clark et al., 2010). In preliminary human trials, NAC treatment caused a decrease in clinical symptoms of PD and an increase in dopamine transporter binding, which is impaired in PD (Monti et al., 2016).

5.4. N-acetyl cysteine and Huntington's disease

Preliminary data suggests that NAC treatment is protective in HD models due to its ability to counter oxidative stress and mitochondrial dysfunction, which both contribute significantly to HD pathogenesis (Li et al., 2010; Sandhir et al., 2012; Stack et al., 2008) (Table 4). Chronic NAC administration is protective in the R6/1 mouse model of HD. Treatment delays the onset of HD-associated motor deficits, and, through cysteine supplementation, improves the glutamatergic dysfunction that underlies depressive behavior in HD (Wright et al., 2015).

5.5. N-acetyl cysteine and amyotrophic lateral sclerosis

NAC is protective in certain models of ALS, however, it has no significant effect in human ALS patients (Table 5). In human neuroblastoma SH-SY5Y cells expressing mutant SOD1 (G93A), increased cytosolic and mitochondrial ROS production is observed (Beretta et al., 2003). NAC treatment reverses the observed mitochondrial impairment (Beretta et al., 2003). Furthermore, NAC treatment of SOD1 transgenic mice improved survival and delayed onset of motor deficits (Andreassen et al., 2000). Despite promising results in ALS models, clinical trials testing NAC as a potential treatment for ALS have been less successful. ALS patients show no significant difference in neuronal survival and/or disease progression with NAC treatment (Deepmala Slattery et al., 2015).

6. Curcumin

Curcumin is an extract from the spice turmeric, which belongs to the ginger family. Curcumin has been commonly used in herbal medicine in Asia for its anti-inflammatory, antioxidant, and analgesic properties (Hewlings and Kalman, 2017). Therefore, it has been studied as a potential therapeutic for various diseases and conditions (Gupta et al., 2013). Curcuminoids, which includes curcumin and its related compounds such as tetrahydroxycurcumin, demethoxycurcumin and bis-demethoxycurcumin have also been tested as longevity-promoting compounds. Curcumin acts through various mechanisms; it decreases levels of reactive oxygen species (ROS) (Dai et al., 2018; Maugeri et al., 2018; Tapia et al., 2014) and has a variety of immunomodulatory activities, such as regulating B-cells, T cells, and macrophage activities (Churchill et al., 2000; Yadav et al., 2005). Curcumin also reduces pro-inflammatory cytokines (Jin et al., 2007; Panahi et al., 2016), potentially through inhibition of the NF-κB inflammatory pathway (Singh and Aggarwal, 1995). Additionally, curcumin also affects epigenetic regulation of gene expression by methods such as inhibiting DNA methylation (Liu et al., 2009) and increasing histone acetylation (Chen et al., 2007; Liu et al., 2005). While studies investigating the lifespan and neuroprotective effects of curcumin show a beneficial effect, it is important to note that these studies are relatively sparse compared to studies on other compounds discussed, and further research needs to be conducted.

6.1. Effect of curcumin on lifespan

Curcumin generally increases lifespan in the animal models tested (Table 1). In *C. elegans*, curcumin increases lifespan as well as increases resistance to oxidative stress (Liao et al., 2011). A recent study using a synthetic curcumin derivative, Cur2004-8, was also found to increase lifespan and increase resistance to oxidative stress to an even greater extent than curcumin. Curcumin also extends the lifespan of Drosophila (Chandrashekara et al., 2014; Lee et al., 2010; Shen et al., 2013; Soh et al., 2013; Suckow and Suckow, 2006), potentially due to the increased resistance to oxidative stress, heat stress, and irradiation (Chen et al., 2018; Lee et al., 2010; Seong et al., 2015). The curcumin derivative tetrahydrocurcumin has been tested in mice and showed mixed results;

one smaller study showed increased lifespan when treatment was given at 13 months of age whereas a subsequent larger study using a lower concentration showed no effect on lifespan when treatment was started at 4 months of age (Kitani et al., 2007; Strong et al., 2013). Because many parameters differed between the two studies (dose, age of intervention, strain of mice, site), it is unclear why the latter study failed to reproduce the effect on lifespan.

6.2. Curcumin and Alzheimer's disease

Curcumin is protective in the AD models tested (Table 2). Curcumin treatment protects against Aβ-induced toxicity and increases oxidative stress in neuroblastoma, endothelial and rat PC12 culture (Kim et al., 2001; Qian et al., 2018). Curcumin can also affect Aβ formation (Ono et al., 2004) and metabolism (Zhang et al., 2010a), as well as reduce levels of Aβ by attenuating the maturation of the precursor protein (Zhang et al., 2010a). Additionally, curcumin decreases activation of microglia and astrocytes (Liu et al., 2016) which is another hallmark of AD. Curcumin treatment on peripheral blood mononuclear cells (PBMCs) derived from AD patients showed a decrease in Aβ levels compared to PBMCs without curcuminoid treatment (Gagliardi et al., 2018). In a recent study, a synthetic curcumin derivative, Cur2004-8, decreased Aβ-induced toxicity in a *C. elegans* model of AD (Niraula and Kim, 2019). In a Drosophila AD model, various curcuminoids rescue eye morphology and locomotor defects (Wang et al., 2014). Similarly, in rodents, curcumin decreases Aβ levels and plaque burden (Garcia-Alloza et al., 2007; Hamaguchi et al., 2009; Lim et al., 2001; Yang et al., 2005). Oxidative damage is reduced with curcumin treatment of rodent models of AD, as indicated by a decrease in oxidized proteins (Lim et al., 2001). Curcumin also reduces pro-inflammatory cytokines and reduces activation of microglia and astrocytes in rodent models of AD (Begum et al., 2008; Liu et al., 2016; Sundaram et al., 2017). Cognitive performance in rodents was improved with curcumin (Cheng et al., 2013; Frautschy et al., 2001; Ma et al., 2009). Curcumin and curcuminoid treatment were also found to supresses the loss of synapses in AD rodent models (Ahmed et al., 2010; Frautschy et al., 2001; Garcia-Alloza et al., 2007). To date, only a few clinical trials have examined the effect of curcumin on AD patients, two of which found no changes in serum Aβ levels or improvement in cognitive ability (Baum et al., 2008; Ringman et al., 2012).

6.3. Curcumin and Parkinson's disease

Curcumin is generally protective in the PD models tested (Table 3). Oxidative stress is strongly associated with PD. Curcumin protects against oxidative stress through reducing lipid oxidation and reducing levels of malondialdehyde (Rascón et al.), H_2O_2 and ROS in a glutathione-depleted dopaminergic cell line and in a human neuroblastoma cell line (Harish et al., 2010; van der Merwe et al., 2017). Importantly, curcumin pre-treatment rescued cell viability and reduced apoptosis in a human neuroblastoma cell line, possibly through inhibiting caspase-3 (van der Merwe et al., 2017). Curcumin was also found to reduce toxicity by inhibiting apoptosis (Qualls et al., 2014; Sang et al., 2018). Lastly, curcumin and curcuminoids can increase α-synuclein degradation by preventing α-synuclein fibrillization and reducing α-synuclein aggregation (Gadad et al., 2012; Jiang et al., 2013). In various Drosophila models of PD, curcumin improved locomotor activity, reduced oxidative stress, and rescued dopaminergic neurons in the brain (Nguyen et al., 2018; Pandareesh et al., 2016; Siddique et al., 2014). In a rodent 6-hydroxydopamine (6−OHDA) model of PD, curcumin treatment protected against loss of TH + cells and dopamine levels (Du et al., 2012; Zbarsky et al., 2005). Other models such as the Park7 (DJ-1) knockout model, the copper intoxication model, and the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model also found that curcumin protected against neuronal apoptosis and improved motor deficits (Abbaoui et al., 2017; Chiu et al., 2013; Pan et al., 2012). Other studies in rodent PD models support the antioxidant role (Khatri and Juvekar, 2016; Wang et al., 2017) and anti-inflammatory role (Sharma and Nehru, 2018) of curcumin.

6.4. Curcumin and Huntington's disease

Curcumin is beneficial in models of HD (Table 4). Curcumin protects against polyQ-mediated photoreceptor neuron degeneration and locomotor dysfunction in Drosophila models of HD (Chongtham and Agrawal, 2016; Ringman et al., 2012). In a CAG140 knockin mouse model of HD, curcumin protects the striatum, and rescues rearing behaviour (Hickey et al., 2012). In an R6/2 mouse model of HD, curcumin also protects the striatum, reduces mHtt levels, and improves motor function (Elifani et al., 2019).

6.5. Curcumin and amyotrophic lateral sclerosis

Curcumin is protective in ALS models (Table 5). Using a motor neuron-like cell model of ALS (NCS-34 transfected with TDP-43), curcumin treatment rescued the abnormal excitability in the cells, such as higher firing frequency and lower threshold of action potential (Dong et al., 2014). In a clinical study, curcumin prevented the decline of motor functions as measured by the ALS Functional Rating Scale (ALS-FRS-r). The treatment group also showed improved ability to handle oxidative stress (Chico et al., 2018). Lastly, curcumin treatment significantly improved survival in patients who were also taking riluzole, compared to patients who were only taking riluzole alone (Ahmadi et al., 2018). However, other functional measures such as ALSFRS-R score, and muscle strength did not differ between the groups (Ahmadi et al., 2018).

7. Discussion

Metformin, resveratrol, rapamycin, NAC, and curcumin all increase lifespan in *C. elegans*, and all but metformin also increase lifespan in Drosophila (Table 1). In mice, the effect of these compounds on lifespan is more complicated, except for rapamycin, which has the most reproducibly beneficial effect on mouse longevity. While both metformin and curcumin have been shown to increase lifespan in mice, other studies have failed to reproduce this finding. In the case of NAC, it may be acting indirectly by decreasing food consumption thereby leading to dietary restriction. Resveratrol has only been shown to increase lifespan in mice maintained on a high fat diet. While examining the effects of these compounds on lifespan in mice has produced mixed results, the fact that at least one study has observed a significant increase in lifespan for each compound demonstrates that all of these compounds can increase lifespan in mammals, but, in some cases only under certain experimental conditions (dose, environment, strain, diet, etc.). Additional studies would be required to determine the precise reasons why the compounds increase lifespan in one experiment but not another, but these studies are time consuming and costly to perform in mice. Currently, it remains unknown whether these compounds can affect longevity in healthy humans.

Similar to their effect on longevity, the effect of these lifespan-extending compounds in models of neurodegenerative disease is more complicated in mammals than in simpler model organisms. Metformin, resveratrol, rapamycin, NAC, and curcumin have all been shown to improve deficits in cellular, *C. elegans* and Drosophila models of neurodegenerative diseases (Tables 2–5). Although many studies support the beneficial effects of these compounds in rodents, and in some cases humans, other studies fail to show a benefit. In cases where a compound fails to show a benefit, the reasons for failure are often unclear. It is possible that a difference in one or more of the experimental conditions can account for the contradictory results. However, without further experimentation, it is hard to determine which factors if any are responsible for the differing outcomes. When an experiment does not

reproduce a beneficial effect observed by others, it could simply be that the experiment failed for one of the several possible reasons that can arise when a compound and a complex organism are involved (e.g. wrong dose of compound, compound doesn't reach target tissue, compound delivery began at the wrong time point, experimenter error etc.). At the same time, it is also possible that neutral or negative studies are not published leading to a reporting bias.

To better understand why differing results are sometimes obtained, it may be important to elucidate the precise mechanisms by which the lifespan-extending compounds provide protection. One important question would be to determine how the neuroprotective effects of these compounds are related to their effects on aging. While we have hypothesized a simple relationship in which aging contributes to neurodegeneration and these compounds are neuroprotective because they delay aging, it is also possible that these compounds impact aging and neurodegeneration independently. Another possibility is that neurodegeneration is part of the aging process such that any impact that these compounds have on aging will necessarily also affect neurodegeneration.

The fact that each of the lifespan-extending compounds reviewed here can be protective in multiple different neurodegenerative diseases suggests the possibility that by targeting the aging process it may be possible to delay or prevent multiple diseases simultaneously. The idea of targeting aging as a cause of disease rather than studying individual diseases is the focus of the growing field of geroscience (Kennedy et al., 2014). As in the neurodegenerative diseases discussed here, aging is the main risk factor for a multitude of diseases, including cardiovascular disease and many forms of cancer. The goal of geroscience is to gain insight into the aging process and use that knowledge to delay or prevent changes that take place during normal aging. By intervening in the aging process, a single treatment may have a beneficial effect on a wide range of diseases in which aging contributes to disease pathogenesis.

8. Conclusions

In this review, we have shown that five different compounds that increase lifespan can be protective in four different neurodegenerative diseases. This suggests the possibility that compounds that increase lifespan may provide novel treatment strategies for these devastating disorders. For this to happen, it will be important to determine why these compounds are neuroprotective in some studies but not others, and why the beneficial effects have not, for the most part, translated into humans. In addition to the compounds reviewed here, there are a number of other compounds that have been shown to extend longevity, many of which have also been shown to be protective in models of neurodegenerative disease. Screening these compounds in cell culture and invertebrate models of neurodegenerative disease would allow for a rapid and cost-effective means to prioritize lifespan-extending compounds for further study in mammals.

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