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Caloric Restriction Mimetics against Age-Associated Disease: Targets, Mechanisms, and Therapeutic Potential

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The increase in life expectancy has boosted the incidence of age-related pathologies beyond social and economic sustainability. Consequently, there is an urgent need for interventions that revert or at least prevent the pathogenic age-associated deterioration. The permanent or periodic reduction of calorie intake without malnutrition (caloric restriction and fasting) is the only strategy that reliably extends healthspan in mammals including non-human primates. However, the strict and life-long compliance with these regimens is difficult, which has promoted the emergence of caloric restriction mimetics (CRMs). We define CRMs as compounds that ignite the protective pathways of caloric restriction by promoting autophagy, a cytoplasmic recycling mechanism, via a reduction in protein acetylation. Here, we describe the current knowledge on molecular, cellular, and organismal effects of known and putative CRMs in mice and humans. We anticipate that CRMs will become part of the pharmacological armamentarium against aging and age-related cardiovascular, neurodegenerative, and malignant diseases.

Caloric Restriction Improves Health

Caloric restriction (CR) consists of the chronic reduction of total calorie intake without malnutrition. Together with intermittent fasting (which can be regarded as a particular form of CR in which episodes of *ad libitum* feeding are alternated with episodes of up to zero caloric uptake), CR is the only known strategy to robustly improve health- and lifespan in most, if not all, living organisms. In Rhesus monkeys, two differently designed studies revealed contrasting results on lifespan (Mattison et al., 2017) but similar health benefits and delayed onset of aging phenotypes. In humans, CR has been reported to counteract several age-associated alterations (Figure 1). In non-obese, healthy adults, 24 months of continuous CR (15%–25%) was safe (Romashkan et al., 2016), improved the quality of life (Martin et al., 2016), and caused 10%–13% weight loss (mostly, but not exclusively, reducing fat mass), which stabilized after 1 year (Redman et al., 2018). Fasting insulin levels, body temperature (a possible marker for metabolic rate), resting energy expenditure, oxidative stress, and thyroid axis activity were reduced under CR (Il'yasova et al., 2018; Redman et al., 2018). "Metabolic adaptation," a long-term effect of CR that reduces the metabolic rate below the expected value, occurs in humans and may support longevity (Heilbronn et al., 2006; Redman et al., 2018). In healthy humans, CR also decreases the levels of circulating tumor necrosis factor-α and cardiometabolic risk factors (triglycerides, cholesterol, and blood pressure) (Most et al., 2018; Ravussin et al., 2015). Upon CR and weight loss, insulin growth factor-1 (IGF1) levels and insulin resistance are reduced in obese patients (Dubé et al., 2011). However, they are not improved in non-obese humans after the 1-year weight loss phase (Most et al., 2018) (contrary to mouse studies) unless protein intake is also reduced (Fontana et al., 2008). While CR inhibits inflammation, its effects on immunity need further clarification since different levels of CR may subvert and/or modulate immune defenses against bacterial (Tang et al., 2016) and viral infection (Wang et al., 2016). In obese humans, CR promotes significant weight loss and improves general health (Ard et al., 2017). Of note, the well-documented good health and high incidence of centenarians in the population of the Japanese Okinawa island have been attributed to nutritional cues including a mild and consistent CR (~10%–15%) (Willcox and Willcox, 2014).

Molecular Effects of CR and Fasting

Macroautophagy (hereafter referred to as autophagy) is a conserved cellular recycling program that eliminates dysfunctional organelles, proteins, and aggregates from the cytoplasm, hence protecting cellular functionality and integrity. Accordingly, impaired or dysregulated autophagy has been linked to advanced age, neurodegeneration, cardiovascular diseases (CVDs), and cancer. In turn, the activation of autophagy via genetic or pharmacological means extends lifespan and/or

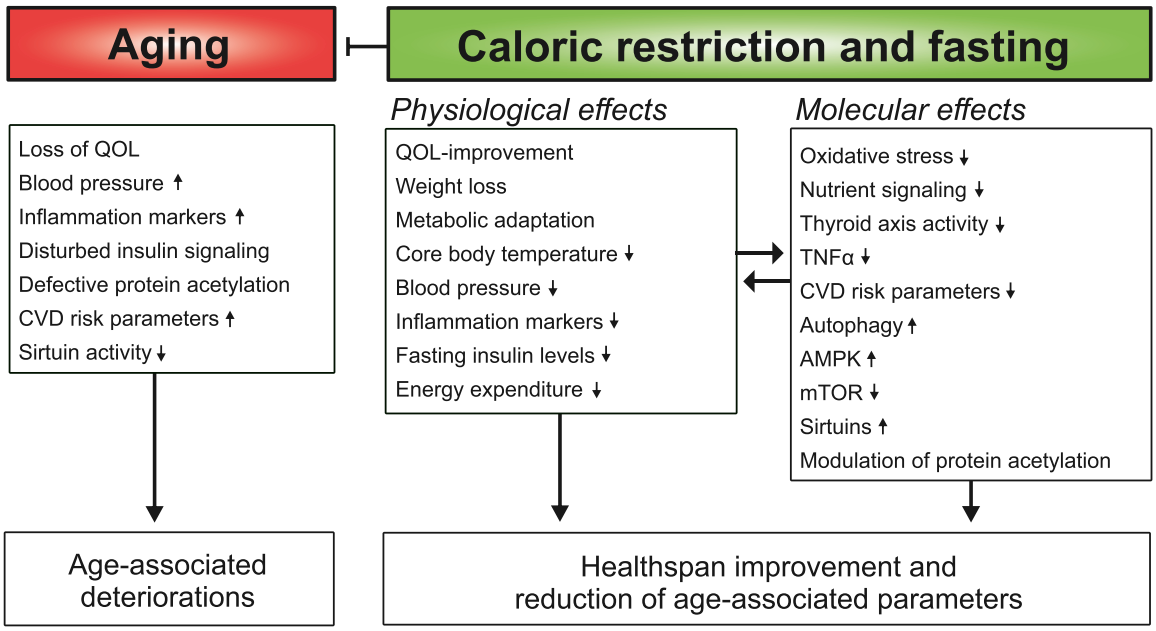

Figure 1. Physiological and Molecular Effects of Caloric Restriction
Caloric restriction reverses aging-derived effects by igniting numerous pathways involved in the improvement of health parameters. AMPK, AMP-activated protein kinase; CVD, cardiovascular disease; mTOR, mechanistic target of rapamycin; TNFα, tumor necrosis factor alpha; QOL, quality of life.

healthspan in numerous model organisms, including mice (Eisenberg et al., 2009). As a catabolic process, autophagy is induced upon nutrient deprivation and plays an important role in the beneficial effects exerted by CR and fasting regimens. CR modulates several molecular key players involved in the regulation and execution of autophagy, nutrient signaling, and energy metabolism (Figure 1). For instance, CR activates AMP-activated protein kinase (AMPK) (Cantó and Auwerx, 2011). AMPK is an energy sensor that inhibits the kinase activity of mechanistic target of rapamycin (mTOR), an autophagy repressor, under CR. Furthermore, CR directly and indirectly activates sirtuins (SIRTs), which are nicotine adenine dinucleotide (NAD^+)-dependent lysine deacetylases (KDACs) and play central roles during aging and autophagy (Guarente, 2007). SIRT1 and AMPK may engage in a positive feedforward loop to amplify the response to CR.

Protein acetylation is a major regulator of autophagy. The Nε-acetylation of lysines is a phylogenetically conserved, post-translational protein modification that is catalyzed by lysine acetyltransferases (KATs) and reversed by KDACs. Nε-acetylation regulates multiple metabolic enzymes, facilitating the adaptation to nutrient availability. Of note, Nε-acetylation may occur in a non-enzymatic fashion in the presence of AcCoA, especially at an acidic pH (James et al., 2017). There are four ways to diminish Nε-acetylation of proteins: (1) by reducing the concentration of cytosolic AcCoA, the sole donor of acetyl groups used by KATs, e.g., via inhibition of its synthesis from glycolysis, β-oxidation of fatty acids, or the catabolism of branched amino acids, or via increase of its consumption, for instance by carnitine acetyltransferases that transfer AcCoA acetyl groups on carnitine; (2) by degrading S-acetyl glutathione by mitochondrial thioesterase glyoxalase 2, GLO2, or cytosolic GLO1, thus reducing intermediates for non-enzymatic Nε-acetylation; (3) by activating specific KDACs, mostly SIRTs; and (4) by inhibiting KATs such as E1A-binding protein p300 (EP300). Notably, SIRT1 activity is low in aged and obese mice. This correlates with the inhibitory hyperacetylation of SIRT3, and transgenic activation of SIRT3 may improve the hepatic consequences of obesity including glucose intolerance (Kwon et al., 2017). Moreover, in mice, transgene-enforced overexpression of SIRT6 (Kanfi et al., 2012) or brain-specific expression of SIRT1 (Satoh et al., 2013) is sufficient to extend lifespan. In an earlier study, however, whole-body overexpression of SIRT1 did not extend lifespan (Herranz et al., 2010). Similarly, another report observed no lifespan extension upon overexpression of the SIRTs sir-2.1 and dSir2 in the nematode *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster*, respectively (Burnett et al., 2011), thus contradicting previous results (Bauer et al., 2009; Rogina et al., 2002; Tissenbaum and Guarente, 2001). While it seems clear that SIRTs exert important functions related to healthy aging, their specific role in promoting longevity remains to be clarified (Dang, 2014).

Interestingly, autophagy and protein acetylation are subjected to circadian fluctuations (Sato et al., 2017). This oscillation is lost with aging and has been proposed as a modulatory target of CR (Sato et al., 2017). The maintenance of rhythmic (de)acetylation by CR is hypothetically linked to increased NAD^+ levels, coupled to SIRT1 activation and rhythmic changes in the inhibitory acetylation of acetyl-CoA-generating acyl-CoA synthase short-chain family member 1 (ACSS1) (Sato et al., 2017). In aged flies, protein acetylation is increased, a phenomenon that can be attenuated by reducing the AcCoA-generating enzyme ATP citrate lyase (ACLY) or by mutating the KAT Chameau, resulting in an extended lifespan (Peleg et al., 2016). Similarly, the inhibitory

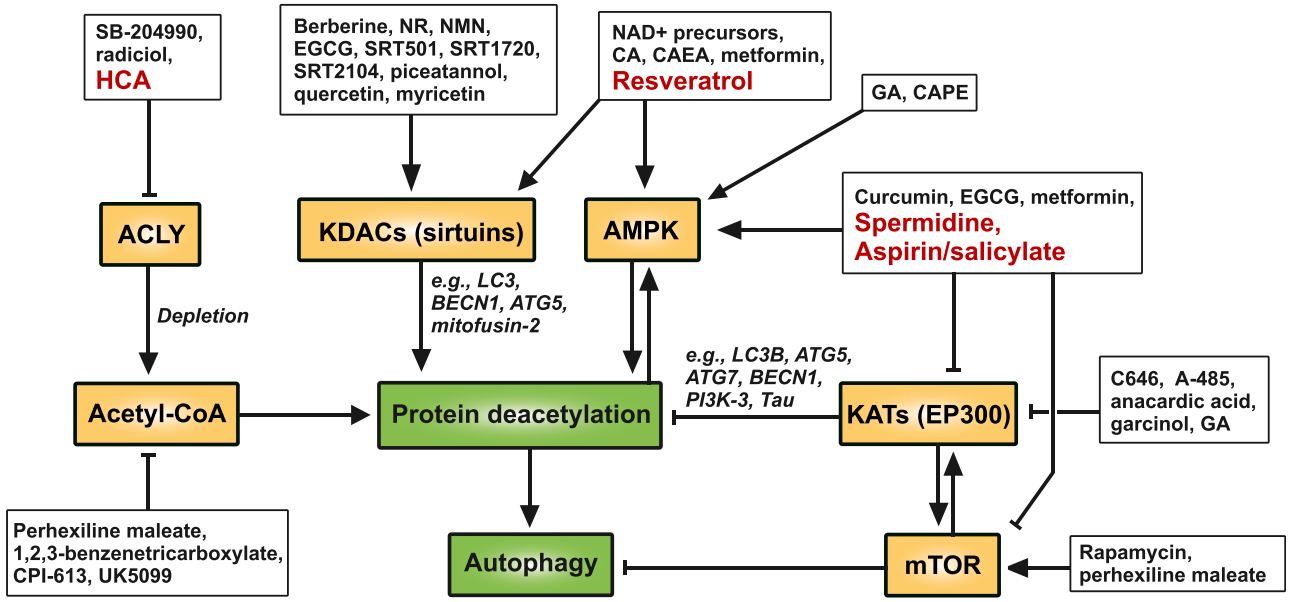

Figure 2. Mechanistic Targets of Known and Potential CRMs

The displayed compounds (known CRMs shown in red, potential CRMs in black) converge in protein deacetylation via acetyl-CoA depletion, inhibition of acetyltransferases, or stimulation of deacetylases, ultimately resulting in autophagy activation. Moreover, AMP-activated protein kinase (AMPK) and mechanistic target of rapamycin (mTOR) represent further targets of CRMs, the pro-autophagic activity of which is intertwined with protein deacetylation processes. ACLY, ATP citrate lyase; BECN1, Beclin 1; CA, caffeic acid; CAEA, caffeic acid ethanolamide; CAPE, caffeic acid phenyl ester; EGCG, Epigallocatechin-3-gallate; GA, gallic acid; HCA, hydroxycitric acid; KATs, lysine acetyltransferases; KDACs, lysine deacetylases; NMN, nicotinamide mononucleotide; NR, nicotinamide riboside; PI3K-3, phosphatidylinositol 3-kinase catalytic subunit type 3.

hyperacetylation of the pro-autophagic transcriptional factor Foxo1 has been observed in aged mouse hearts (Ren et al., 2017). Moreover, CR deacetylates histones H3 and H4 in mouse fat pads (Xu et al., 2015) and reduces the levels of biotin, which acts as an endogenous inhibitor of SIRT1 (Xu et al., 2015). Both histone deacetylation and deacetylation of cytosolic proteins may affect the expression and activity, respectively, of autophagy-relevant proteins (Eisenberg et al., 2009; Mariño et al., 2014). Both in mice and in humans, acute starvation causes a reduction of the acetylation of cytoplasmic proteins in peripheral blood mononuclear cells (Pietrocola et al., 2017). However, every-other-day fasting increases histone acetylation in the mouse retina (Guo et al., 2016), and acetylation is reduced in aged mouse livers, a phenomenon that is reversed by CR, which causes hepatic protein hyperacetylation (Sato et al., 2017). This is at odds with chronic alcohol abuse, which leads to NAD^+ depletion and SIRT inhibition, resulting in hyperacetylation of multiple proteins in the liver (such as AMPK, β-catenin, histone H3, and the transcription factors SREBB2, PPARα, FOX01, NFκB, and NFAT) (French, 2016). Therefore, the impact of CR on acetylation might depend on tissue, cell type, and the precise protein species. Indeed, one study reports that CR causes hyperacetylation of mitochondrial proteins in the liver and reduces acetylation in brown adipose tissue, yet it fails to affect the acetylation of mitochondrial proteins from other tissues (Schwer et al., 2009).

CR Mimetics

Despite the uncontestable health-promoting effects of CR, most individuals are unable to observe a CR lifestyle, likely explaining some failures in observational clinical studies (Redman et al., 2018). Although long-term compliance may be improved by periodic fasting regimens, pharmacological approaches that induce autophagy without the subjective discomfort linked to CR or periodic fasting are warranted. Indeed, several CR mimetics (CRMs) improve health parameters in rodents and humans (see below). We previously defined CRMs as compounds that activate autophagy by promoting the deacetylation of cellular proteins (Madeo et al., 2014), by (1) depleting AcCoA, (2) inhibiting acetyltransferases, and/or (3) stimulating deacetylases (Figure 2).

This definition reflects the fact that protein acetylation usually inhibits autophagy, while protein deacetylation favors autophagy. For instance, starvation is coupled to the inhibition of the acetyltransferase EP300 (due to the depletion of AcCoA), as well as to the activation of the deacetylase SIRT1 (due to the increase of the NAD^+/NADH ratio and the activation of AMPK). This results in the deacetylation of hundreds of cellular proteins (Morselli et al., 2011), reflecting multipronged regulatory effects on cell metabolism and the autophagic cascade. A systematic screen for KATs, the inhibition of which would induce autophagy, led to the identification of EP300 as a major negative regulator of autophagy that acts epistatic to starvation (Mariño et al., 2014).

Interestingly, EP300 is subjected to activating phosphorylation by mTORC1 (Wan et al., 2017), while conversely, inhibition of EP300 generally results in mTORC1 inhibition (Pietrocola et al., 2015), suggesting that both regulatory systems are intertwined. Similarly, protein deacetylation may be connected to the activation of AMPK, a potent autophagy inducer. Thus, deacetylation

of liver kinase B1 (LKB1), for instance by SIRT2, favors the LKB1-mediated activation of AMPK (Tang et al., 2017). Likewise, EP300 inhibition results in AMPK activation (Pietrocola et al., 2015). These examples illustrate how protein deacetylation may initiate autophagy, correlating with mTORC1 inhibition and AMPK activation. However, EP300 inhibition results in the induction of autophagy even in conditions in which AMPK is deleted, mTORC1 is artificially activated, or ULK1 is inhibited (Pietrocola et al., 2018; Su et al., 2017). This suggests that protein deacetylation can set off the autophagic cascade in a dominant fashion that is largely independent of other regulatory systems.

In accord with this interpretation, EP300 inhibition or SIRT activation may favor autophagy through deacetylation reactions that affect multiple autophagy-executory proteins (Pietrocola et al., 2015). For instance, EP300 inhibition results in the deacetylation of phosphatidylinositol 3-kinase catalytic subunit type 3 (PI3K3) at K29 and K771, favoring its interaction with allosteric activators contained in the pro-autophagic Beclin 1 (BECN1) complex and its substrate phosphatidylinositol, respectively (Su et al., 2017). BECN1 itself is also a substrate of EP300 and SIRT1 (at K430 and K437), and deacetylation of BECN1 favors the dissociation of its inhibitory interactor Rubicon (Sun et al., 2015). Of note, pro-autophagic derepression of BECN1 has been recently shown to promote longevity in mice (Mariño et al., 2014). Furthermore, SIRT1 deacetylates nuclear microtubule-associated proteins 1A/1B light chain 3B (hereafter referred to as LC3) (at K49 and K51), stimulating its interaction with the nuclear protein DOR and its export to the cytoplasm, where it acts as a key initiator of autophagy (Huang et al., 2015). EP300 can also acetylate ATG5 and ATG7, both of which are involved in a conjugation system that promotes LC3 lipidation, which is required for autophagy induction. Of note, ATG5 is also deacetylated by SIRT2, supporting the notion that many autophagy regulators are substrates of both EP300 and SIRTs (Liu et al., 2017a).

While the link between deacetylation of cytoplasmic proteins and autophagy seems rather unambiguous, it appears less straightforward with respect to nuclear proteins. On the one hand, the pro-autophagic transcriptional response has been linked, for example, to SIRT1- and spermidine-induced deacetylation of histones H4 and H3 (Eisenberg et al., 2009), respectively. On the other hand, glucose deprivation stimulates AMPK activation with the final result that acetyl-CoA synthetase 2 (ACSS2) phosphorylated by AMPK translocates to the nucleus where it interacts with the transcription factor EB (TFEB) and binds to promoter regions of autophagy genes, locally producing acetyl-CoA and favoring pro-autophagic H3 hyperacetylation (Li et al., 2017b). These divergent outcomes may reflect feedback loops that impose a self-limitation on the autophagic process. For instance, rapamycin-induced autophagy is coupled to the hypoacetylation of H4K16 following the downregulation of lysine acetyltransferase 8 (KAT8), thereby reducing the transcription of pro-autophagic genes (Füllgrabe et al., 2013).

Besides autophagy-regulatory and executory proteins, deacetylation may also affect autophagic substrates. Depletion of general control of amino acid synthesis 5 (GCN5) like-1 (GCN5L1), a component of the mitochondrial acetyltransferase machinery, leads to mitochondrial protein deacetylation catalyzed by SIRT3, thus favoring mitophagy (Webster et al., 2013). SIRT1 deacetylates mitofusin-2, a protein tethered to the mitochondrial membrane, facilitating SIRT1-induced autophagy and mitophagy (Biel et al., 2016). As a further example, EP300 inhibition reduces the acetylation of Tau (a protein that forms pathogenic intraneuronal aggregates in Alzheimer's disease), which favors its clearance by autophagy (Min et al., 2015).

Bona fide CRMs and Candidate CRMs

Several agents may be considered as CRMs since they cause protein deacetylation deriving in autophagy induction (Figure 2). We suggest that CRMs should also have the capacity to reproducibly extend lifespan and/or healthspan in model organisms, hence extending the functional definition of CRMs by another criterion. Here, we enumerate compounds that either fully comply with these stringent criteria (*bona fide* CRMs) or that do so at least partially according to the current state-of-the-art (potential CRMs) (Table 1).

Resveratrol and Other SIRT1 Activators

Resveratrol is a polyphenolic phytoalexin that is particularly abundant in the skin of grapes and in red wine. It has been shown to promote longevity across species and to improve age-related parameters in mice. However, resveratrol seems to only prolong the lifespan of mice on a high-fat diet (HFD) (Baur et al., 2006), but not on regular chow. Still, resveratrol exerts a number of protective effects in mammalian models of metabolic syndrome, type 2 diabetes (an effect that is enhanced when resveratrol is combined with metformin), cancer, neurodegeneration, and CVD (Rajman et al., 2018). However, contrary findings have been reported recently on its efficacy against metabolic syndrome (Kjær et al., 2017). Interestingly, resveratrol can counteract the reduction of duodenal SIRT1 levels in rats fed an HFD, which is accompanied by improved insulin sensitivity (Côté et al., 2015). This indicates the potential of resveratrol as an agent to counteract obesity- and diabetes-induced insulin resistance as well as dysregulated glucose homeostasis. Moreover, resveratrol induces a CR-like transcriptional signature in mice and recapitulates metabolic changes of CR in humans (Timmers et al., 2011).

Several studies have examined resveratrol on primates, also showing SIRT1 induction, NF-κB repression, improved insulin signaling, and attenuated inflammation in adipose tissue of high-fat, high-sugar (HFS)-fed animals (Rajman et al., 2018), coupled to reduced CVD risk parameters induced by HFS (Mattison et al., 2014). A large number of clinical trials assessing its effects on cancer, diabetes, obesity, non-alcoholic fatty liver (NAFL), neurological disease, and CVDs have been performed with mostly beneficial outcomes.

Resveratrol targets a number of stress-related cellular components, including AMPK (Rajman et al., 2018), which might represent a major molecular target, and the NAD^+-dependent deacetylase SIRT1. Both AMPK and SIRT1 have been shown to be required for resveratrol-induced health promotion (Lagouge et al., 2006; Price et al., 2012). Resveratrol can stimulate SIRT1 (possibly indirectly), resulting in general protein deacetylation and autophagy induction (Morselli et al., 2010, 2011; Pietrocola et al., 2012).

Although a *bona fide* CRM, resveratrol is afflicted by rather low systemic availability and absorption. One strategy to improve

Table 1. Classification of Protective Substances as CRMs, Potential CRMs, and Other Compounds

Group	Substance	(Major) Molecular Target(s)	(Nutritional) Sources	Clinical Trials[a]
CRMs	aspirin (and salicylate)	AMPK, EP300, COX-1, COX-2, mTOR, NF-kB	willow bark, synthetic	several meta-analyses available, e.g., Cuzick et al., 2015; Raju et al., 2016
	hydroxycitric acid	ACLY	diverse tropical plants, *Garcinia cambogia*, and *Hibiscus sabdariffa*	meta-analyses on weight loss through HCA in Onakpoya et al., 2011; NCT00699413 and NCT01238887
	resveratrol	KDACs (SIRT1), AMPK, NF-κB	fruits, plants, and skin of grapes	reviewed in Berman et al., 2017, e.g., NCT02621554
	spermidine	KATs (EP300), mTOR, AMPK	wheat germs, soybeans, and nuts	safety evaluation in Schwarz et al., 2018; neuroprotection (Wirth et al., 2018); NCT02755246, NCT03378843, and NCT03094546
Potential CRMs	1,2,3-benzenetricarboxylate	citrate transport protein	synthetic	–
	acipimox	niacin receptor 1	synthetic	several studies on obesity and diabetes, e.g., NCT00549614, NCT01488409, NCT00943059, and NCT01816165
	berberine	SIRT1	*Berberis vulgaris* and several other plants (roots and bark)	numerous phase 3 and 4 studies; reviewed in Imenshahidi and Hosseinzadeh, 2016
	caffeic acid	AMPK and sirtuins	eucalyptus bark	7 studies registered, e.g., NCT03070262; the clinical potential of CAPE reviewed in Murtaza et al., 2014
	catechin	pleiotropic, exact mechanism unknown	cocoa, tea, and red wine	mainly green-tea combinations tested, few single compound studies; reviewed in Chacko et al., 2010; e.g., NCT03213340, NCT00233935, and NCT00448513
	curcumin	AMPK, mTOR, and EP300	*Curcuma longa*	numerous including phase 3 and 4 studies; reviewed in Gupta et al., 2013; e.g., NCT03085680, NCT01052025, NCT01975363, and NCT00099710
	epicatechin	pleiotropic, exact mechanism unknown	cocoa, tea, and red wine	numerous studies using catechin-rich extracts, few single component trials, e.g., NCT01856868, NCT01880866, NCT02221791, NCT01691404, NCT02490527, and NCT02292342
	EGCG	AMPK, mTOR, HATs, and KDACs	green tea	numerous phase 3 and 4 studies; reviewed and discussed in Mereles and Hunstein, 2011
	gallic acid	AMPK and HATs	black tea and various plants	mainly polyphenolic combinations tested, e.g., NCT02800967, NCT02005939, and NCT03214276
	metformin	AMPK, mTOR, HATs, and KDACs (sirtuins)	French lilac (*Galega officinalis*)	numerous phase 3 and 4 studies, reviewed in Nasri and Rafieian-Kopaei, 2014; e.g., NCT02432287
	myricetin	SIRT1	black tea, cole, parsley, garlic, curcuma, and fruits	reviewed in Li and Ding, 2012
	NAD^+	KDACs (sirtuins), AMPK	various food	reviewed in Fang et al., 2017; many studies supplementing precursors, especially NR
	nicotinamide	KDACs (sirtuins)	various food	numerous, e.g., NCT02213094, NCT02416739, NCT03061474, and NCT01250990
	nicotinamide mononucleotide	KDACs (sirtuins)	various food	NCT03151239 and UMIN000021309 (NIPH, Japan)
	nicotinamide riboside	KDACs (sirtuins)	various food	numerous studies, including phase 3 and 4; reviewed in Rolfe, 2014, e.g., NCT03423342, NCT03423342, and NCT02921659
	perhexiline maleate	carnitine O-palmitoyl transferase 1, mTOR	synthetic	numerous; reviewed in Chong et al., 2016
	piceatannol	SIRT1	passion fruit seeds	–
	quercetin	SIRT1	black tea, onions, rocket, cole, curcuma, and fruits	reviewed in Miles et al., 2014; e.g., NCT00065676 and NCT01691404
	rapamycin	mTOR	*Streptomyces hygroscopicus*	numerous; reviewed in Li et al., 2014, e.g., NCT01649960
	SRT1720	SIRT1	synthetic	–
	UK5099	mitochondrial pyruvate carrier	synthetic	–

(*Continued on next page*)

Table 1. *Continued*

Group	Substance	(Major) Molecular Target(s)	(Nutritional) Sources	Clinical Trials[a]
Others	4,4′-dimethoxychalcone	GATA transcription factors	*Angelica keiskei*	–
	A-485	EP300	synthetic	–
	acarbose	α-glucosidase	bacterial (*Streptomyces, Actinoplanes*)	numerous including phase 3 and 4 studies; e.g., NCT02865499, NCT02953093, and NCT01490918
	anacardic acid	EP300	cashew nutshell, *Anacardium occidentale*	–
	C646	EP300	synthetic	–
	CAEA	AMPK, sirtuins	synthetic	–
	CAPE	AMPK	propolis	clinical potential reviewed in Murtaza et al., 2014
	CPI-613	pyruvate dehydrogenase	synthetic	several phase 2 studies; e.g., NCT01835041, NCT03370159, and NCT01902381
	garcinol	EP300	*Garcinia indica*	–
	glucosamine	hexokinase and mTOR	crustaceans, cartilage	numerous studies on arthritis, reviewed in Ogata et al., 2018; e.g., NCT02448199
	radicicol	ACLY and HSP90	*Monosporium bonorden*	–
	SRT501	SIRT1	see resveratrol	reviewed in Berman et al., 2017
	SB-204990	ACLY	synthetic	–
	SRT2104	SIRT1	synthetic	several phase 1 studies; three phase 2 studies registered: NCT01018017, NCT01154101, and NCT01018017

Classification was based on whether compounds are known (1) to induce protein deacetylation that is causal for protective autophagy and to exert health-promoting effects in higher models (CRMs), (2) to promote protective autophagy and have molecular targets involved in protein deacetylation (potential CRMs), and (3) to exert protective effects without evidence for either autophagy induction or protein deacetylation (others). ACLY, ATP citrate lyase; AMPK, AMP-activated protein kinase; CAEA, caffeic acid ethanolamide; CAPE, caffeic acid phenyl ester; COX, cyclooxygenase; EGCG, epigallocatechin-3-gallate; EP300, E1A-binding protein p300; HCA, hydroxycitric acid; HSP90, heat shock protein 90; KATs, lysine acetyltransferases; KDACs, lysine deacetylases; mTOR, mechanistic target of rapamycin; NF-kB, nuclear factor "kappa-light-chain-enhancer" of activated B-cells; SIRT1, sirtuin (silent mating type information regulation 2 homolog) 1.

[a]If applicable, reviews and meta-analyses, or examples of advanced clinical studies, are depicted, indicating the current average phase of trials; clinicaltrials.gov identifiers, if not stated otherwise

this galenic problem consists in micronization to decreased particle size, yielding the proprietary formulation SRT501.

Other small-molecule activators of SIRT1 have been developed. For instance, SRT1720 has been demonstrated to extend lifespan and improve metabolic syndrome, insulin sensitivity, and endothelial dysfunction in mice (Hubbard and Sinclair, 2014). A related compound, SRT2104, which also extends murine lifespan, has undergone clinical phase I and II trials, revealing only minor adverse effects (Hubbard and Sinclair, 2014). Both SIRT1 activators have been shown to improve healthspan in mice, reducing inflammation and protecting from neurodegeneration (Hubbard and Sinclair, 2014). According to one clinical study, SRT2104 can reduce the serum levels of interleukin-6 and C-reactive protein induced by intravenous injection of lipopolysaccharide (van der Meer et al., 2015). Additional data on SRT2104 effects on human health will likely be reported in the near future.

Spermidine

Spermidine is a polyamine that induces autophagy in different model organisms, including mice (Eisenberg et al., 2009, 2016; Morselli et al., 2011), and this induction is causal for at least some of the observed beneficial effects. For instance, genetic ablation of autophagy abrogates spermidine-mediated lifespan extension in yeast, nematodes, and flies and attenuates cardioprotective effects (Eisenberg et al., 2016) in mice. Spermidine inhibits the activity of several acetyltransferases (Eisenberg et al., 2009), including EP300, and this suffices for autophagy induction (Pietrocola et al., 2015). Intriguingly, these pro-autophagic deacetylation effects are synergistic with those of resveratrol (Morselli et al., 2011), which instead promotes the deacetylase activity of SIRT1 (see above). Moreover, spermidine has been shown to inhibit mTORC1 and activate AMPK (Mariño et al., 2014). It has also been speculated that spermidine might post-translationally hypusinate the translation factor eIF5A, which leads to the synthesis of the pro-autophagy transcription factor TFEB, at least in immune cells (Zhang et al., 2018). Moreover, spermidine can promote mitophagy (a specialized form of autophagy that eliminates damaged or dysfunctional mitochondria) in cell culture (Qi et al., 2016) and mice (Eisenberg et al., 2016). In human cells, this depends on ataxia-telangiectasia mutated protein kinase (ATM) and consequently on the phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1) (Qi et al., 2016), which has been linked to the promotion of mitophagy (Eiyama and Okamoto, 2015).

Spermidine is naturally produced in the body by cellular biosynthesis as well as by the intestinal microbiota. In addition, oral ingestion of spermidine contained in food items like wheat germs, soybeans, or nuts among others, results in a

good bioavailability (Soda et al., 2009). Besides its role in general cell homeostasis (e.g., stabilization of DNA and RNA, cell growth, and translation regulation), dietary supplementation of spermidine has been associated to manifold health-promoting effects (Madeo et al., 2018). Spermidine feeding promotes lifespan across species, including mice, suppresses tumorigenesis, enhances anticancer immune response, stimulates memory T cell formation, promotes cardioprotection, improves skeletal muscle regeneration, and mediates neuroprotection (Madeo et al., 2018), thus qualifying this polyamine as a CRM. Accordingly, increased levels of whole-blood spermidine are linked to longevity in healthy nonagenarians and centenarians (Pucciarelli et al., 2012). Furthermore, epidemiological studies correlate elevated dietary polyamine uptake with diminished cardiovascular and cancer-related mortality (Eisenberg et al., 2016). That said, increased polyamine levels have also been associated with various human pathologies (Madeo et al., 2018), although this might represent a (non-causal) protective response.

Clinical trials are needed to explore possible contraindications of spermidine administration. A trial on supplementation of spermidine-rich plant extracts to elderly is currently ongoing (www.clinicaltrials.gov identifier: NCT02755246) and suggests good tolerability and safety of the compound (Schwarz et al., 2018). Moreover, a small pilot trial has already revealed the beneficial effects of spermidine supplementation in elderly people with subjective cognitive decline (Wirth et al., 2018).

Hydroxycitric Acid and Other AcCoA-Depleting Agents

Hydroxycitric acid (HCA) acts as a competitive low-affinity inhibitor of ATP citrate lyase (ACLY), which generates cytosolic AcCoA and thus represents an AcCoA-depleting CRM. HCA is present in diverse tropical plants, including *Garcinia cambogia* and *Hibiscus sabdariffa*. HCA salts have been shown to reduce body weight, insulin resistance, and oxidative stress in obese Zucker rats (Asghar et al., 2007). In a mouse model of multiple sclerosis, a garcinia extract containing 50% HCA exerted anti-inflammatory and anti-oxidative effects (Goudarzvand et al., 2016). Furthermore, in mice, HCA improves the antitumor efficacy of immunogenic chemotherapy, which required regulatory depletion of T cells (which dampen anticancer immunity) from the tumor bed (Mariño et al., 2014; Pietrocola et al., 2016) and tumors to be autophagy-competent (Mariño et al., 2014). Indeed, HCA promotes autophagic flux in diverse organs, including the liver, the myocardium, and skeletal muscle, and this induction is required for body weight reduction in mice (Mariño et al., 2014). HCA is an over-the-counter weight-loss drug, and clinical trials have shown its effectivity in obese patients, although only at high doses ($\geq$3 g per day). Nevertheless, several rodent studies showing adverse effects on the male reproductive system upon administration of HCA preparations have incited health concerns.

Another ACLY inhibitor, the synthetic SB-204990, also stimulates autophagy in mice (Pietrocola et al., 2016) and mediates cholesterol and triglyceride reduction as well as tumor growth suppression in rodents (Pietrocola et al., 2016). Possibly, the Cullin3-KLHL25 (Kelch-like family member 25) ubiquitin ligase is responsible for the degradation of ACLY and subsequent inhibition of lipid synthesis and tumor progression (Zhang et al., 2016a). Future evaluation of the lifespan- and healthspan-promoting effects of SB-204990 must determine its potential as a CRM. The ACLY and HSP90 inhibitor radicicol (first isolated from the fungus *Monosporium bonorden*) exhibits diverse protective effects in rodents, e.g., against renal and myocardial ischemia-reperfusion damage, but its pro-autophagic potential remains elusive (Sonoda et al., 2010).

Further synthetic agents capable of depleting AcCoA have been proposed as CRMs. Perhexiline maleate reduces AcCoA levels via inhibition of carnitine O-palmitoyl transferase 1 and is able to reversibly inhibit mTORC1 signaling and to promote autophagy *in vitro* (Balgi et al., 2009). It is a clinically approved anti-anginal agent that exhibits cardioprotective (Phan et al., 2009) and anti-tumor potential (Vella et al., 2015), although putative hepato- and/or neurotoxic effects need to be explored. Furthermore, UK5099 (a mitochondrial-pyruvate-carrier inhibitor) and 1,2,3-benzenetricarboxylate (an inhibitor of citrate transport) cause AcCoA depletion, protein deacetylation, and autophagy (Mariño et al., 2014). However, their *in vivo* effects need further investigation. Similarly, the impact of the pyruvate dehydrogenase inhibitor CPI-613 (a synthetic lipoate analog) on autophagy requires further investigation. CPI-613 has been shown to be tolerable in humans and to exhibit potential anti-tumor and chemotherapy-potentiating activity at pre-clinical and clinical levels (Alistar et al., 2017), whereas a recent phase II trial on small cell lung carcinoma patients failed to show beneficial effects.

NAD^+ Intermediates

NAD^+ concentrations decrease with age in rodents and humans at the systemic level, correlating with the development of age-associated pathologies (Das et al., 2018). Importantly, the overexpression of the NAD^+-generating enzymes CYB5R3 and NQO1 is sufficient to increase murine life- and healthspan (Diaz-Ruiz et al., 2018). Interestingly, supplementation of NAD^+ precursors, in particular nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN), also exerts anti-aging effects (Das et al., 2018). For instance, in rodents, NMN and NR have been shown to cause hepato- and cardioprotective effects (Rajman et al., 2018); alleviate vascular aging (Das et al., 2018); improve learning, memory, and cognitive function in Alzheimer disease models; promote muscle function in models of muscular dystrophy (Rajman et al., 2018); and ameliorate diabetic pathophysiology (Yoshino et al., 2011), among other effects. In fact, NR could extend the lifespan of mice even when administered late in life (Zhang et al., 2016c). NMN and NR are contained in a variety of daily natural food sources, including different vegetables, fruits, meat, and shrimp as well as in human milk.

Nicotinamide (NAM, also called vitamin B3), another NAD^+ precursor, can prevent aging-associated glaucoma in a mouse model (Williams et al., 2017). Chronic feeding with NAM on a low-fat diet or HFD fails to improve longevity but promotes the healthspan of aged mice (Mitchell et al., 2018). Specifically, glucose homeostasis, body fat percentage (on a low-fat diet), and locomotor activity (on HFD) were improved, while steatosis and inflammation were reduced (on HFD) (Mitchell et al., 2018).

Besides direct supplementation of NAD^+ metabolites and precursors, beneficial elevation of NAD^+ levels may also be achieved by interacting with its intracellular generation. A recent report shows that the pharmacological inhibition of the enzyme α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (ACMSD), which is a limiting step in *de novo* NAD^+ synthesis in

the kidney and the liver, might be another possible mode of action for potential CRM-like agents (Katsyuba et al., 2018). The authors also identified two specific inhibitors that could be delivered via chow supplementation (Katsyuba et al., 2018).

At the molecular level, NAD^+ is required for SIRT1 deacetylase activity and is thus instrumental for protein-deacetylation-mediated autophagy induction in general. The NAD^+/SIRT1 route reportedly upregulates autophagy via deacetylation of Atg5, Atg7, and Atg8 in murine neurons (Fang et al., 2017) and stimulates mitophagy (Fang et al., 2017). In addition, NAD^+ has been suggested to induce autophagy via AMPK (Fang et al., 2017). Preclinical safety assessments in rodents have suggested no adverse response upon short- or long-term treatment with NR or NMN (Fang et al., 2017). In the first controlled clinical trial of NR, good bioavailability and increased blood levels of NAD^+ could be detected (Trammell et al., 2016). NAM has been shown in a large phase III trial to reduce the incidence of non-melanoma skin cancers (Chen et al., 2015). Interestingly, treatment with the nicotinic acid analog acipimox (a medication against hyperlipidemia) improved skeletal muscle mitochondrial function in type 2 diabetes patients (van de Weijer et al., 2015). A number of clinical trials are currently underway to assess the efficacy of NAD^+ precursors in humans, especially of NR.

Aspirin

The non-steroidal anti-inflammatory drug acetylsalicylic acid, better known as aspirin, has been in extensive medical use since 1899. Before that, salicylates from willow bark were widely used in folk medicine. Aspirin, which quickly metabolizes to salicylate *in vivo*, has lifespan-increasing effects on model organisms, including mice (Strong et al., 2008), but seems to inhibit growth in yeast (Baroni et al., 2018; Carmona-Gutierrez et al., 2018; Madeo et al., 1997).

Salicylate inhibits EP300 by competing with acetyl-CoA, thus activating autophagy (Pietrocola et al., 2018). Aspirin also reduces mTOR signaling and activates AMPK and autophagy in colorectal cancer (CRC) cells (Din et al., 2012), which might explain its anti-cancer efficacy. However, contradictory results were reported on cardiac fibroblasts, in which it inhibited autophagy (Liu et al., 2017b). AMPK activation was also found *in vivo* in mice (Hawley et al., 2012) and might represent a major mechanism of aspirin-triggered CRM effects. Recently, aspirin has been suggested as an anti-cancer therapeutic (Patrignani and Patrono, 2016), as continuous intake is associated with lower tumor occurrence and decreased metastasis of CRC and breast and prostate cancer in humans (Patrignani and Patrono, 2016). Mortality-reducing effects were found in several human studies after the long-term use of low doses (3–10 years; circa 75–300 mg/day). Several meta-analyses have suggested aspirin as a primary and secondary prevention therapy of CVD, reducing both the risk for CVDs and mortality. In line, aspirin provided heart protection and improved glucose tolerance in rodents (Liu et al., 2017b). Additionally, mitophagy was induced in cardiomyocytes (Pietrocola et al., 2018) and fat-induced insulin resistance improved in mice (Kim et al., 2001), though opposite effects in humans have been reported (Netea et al., 2001).

The positive effects of long-term aspirin intake might outweigh the risk of negative ones, e.g., gastrointestinal bleeding, if it became possible to exclude patients at risk. Overall, aspirin seems a reasonable and cost-efficient CRM with a high therapeutic potential against multiple diseases but a generally low risk for human health.

(Poly)phenols

In general, phenolic compounds may represent an attractive source of (potential) CRMs. Epidemiological studies have linked an elevated intake of polyphenol-rich food (mostly fruits and vegetables) and drinks (including coffee, tea, and wine) to a reduced incidence of malignant, cardiovascular, and neurodegenerative diseases (Vauzour et al., 2010). Caffeic acid (CA; found in the eucalyptus bark) and gallic acid (GA; found in black tea and many plants), including derivatives thereof, for instance, reportedly induce autophagy (Doan et al., 2015), AMPK activation (Doan et al., 2015; Tyszka-Czochara et al., 2017), protein deacetylation (Pietrocola et al., 2012), extended longevity across species, and anti-diabetes effects (Eid et al., 2017). While GA was found to inhibit EP300 (Lee et al., 2015c), CA might activate SIRTs, namely SIRT3 (Mu et al., 2015). Moreover, CA has been shown to induce autophagy and improve glucose and lipid metabolism as well as renal function in a diabetic rat model (Matboli et al., 2017). Notably, CA phenyl ester (CAPE), an AMPK activator, has broad health-promoting properties and is a major bioactive component of propolis, a honeybee product commonly used in traditional medicine. CAPE has been reported to extend the lifespan of a mouse model of amyotrophic lateral sclerosis (ALS) (Fontanilla et al., 2012). Additionally, an ethanolamide derivative (CAEA) has been shown to activate AMPK as well as SIRTs and ameliorate cardiac damage in a mouse model (Lee et al., 2015b).

Another example is the stilbenoid piceatannol (found, e.g., in passion fruit seeds), an analog of resveratrol, which—along with its metabolite isorhapontigenin—was shown to stimulate SIRT1, activate autophagy (synergistically with resveratrol), deacetylate cytosolic proteins, improve parameters of metabolic syndrome in obese mice, promote murine astrocyte differentiation *in vivo*, and extend the lifespan of worms (Pietrocola et al., 2012; Surh and Na, 2016). However, to our knowledge, lifespan and healthspan data of piceatannol in higher models are elusive.

Curcumin is the major polyphenol in the rhizome of turmeric (*Curcuma longa*) and has a long tradition as a medical herb. Indeed, curcumin feeding extends the lifespan of non-rodent models and exerts cardioprotective, antineoplastic, and antidiabetic effects in rodent models (Rahmani et al., 2018). Dietary curcumin is readily metabolized to tetrahydrocurcumin (THC), which was shown to prolong the lifespan of middle-aged mice (Kitani et al., 2007). Numerous clinical trials have aimed at assessing the health effects of curcumin on humans, with positive effects reported for multiple diseases including different types of cancer, metabolic syndrome, depression, and diabetes (Zheng et al., 2018). Curcumin seems well tolerated and non-toxic. Its poor bioavailability can be significantly increased by several agents, including piperine (Shoba et al., 1998) (a major component in black pepper). The mode of action of curcumin remains to be clarified and—as with other polyphenols—may involve antioxidant properties but also autophagy induction, at least in some pathological settings. Its pro-autophagic activity has been connected to AMPK activation (Xiao et al., 2013) and mTOR signaling (Wang et al., 2014) as well as to inhibition of EP300 (Pietrocola et al., 2015).

A number of polyphenols are known to act as EP300 inhibitors, associated with autophagy induction and health-promoting

effects. These include anacardic acid (AC) (Pietrocola et al., 2015) (from the nutshell of the cashew, *Anacardium occidentale*) and garcinol (Pietrocola et al., 2015) (from the fruit of the Kokum tree, *Garcinia indica*). Similarly, the synthetic EP300 inhibitor C646 induces autophagy (Pietrocola et al., 2015) and exerts protective effects, including immunostimulatory antitumor activity (Liu et al., 2013). However, histone acetyl transferase (HAT) selectivity might be compromised at higher concentrations (van den Bosch et al., 2016). Interestingly, a novel EP300 inhibitor (A-485) shows higher potency as well as HAT selectivity and may suppress tumor growth (Lasko et al., 2017).

Several flavonoids, a multifunctional and highly bioactive polyphenolic subclass, which comprises more than 5,000 plant-derived substances, also promote autophagy coupled to protein deacetylation (Pietrocola et al., 2012). For instance, quercetin (*inter alia* found in black tea, onions, rocket, cole, curcuma, and fruits) and the nutritionally less abundant myricetin (sources: black tea, cole, parsley, garlic, curcuma, and fruits), which only differ in the position of a hydroxy group, were shown to induce autophagy and reduce protein acetylation to the same extent (Pietrocola et al., 2012). Both agents activate SIRT1 (D'Andrea, 2015; Jung et al., 2017) and extend lifespan in worms (DAF-16 dependent) (Büchter et al., 2015; Pietsch et al., 2009). They also promote the survival of neurodegenerative fly models (Ara et al., 2017; Kong et al., 2016), while only quercetin was shown to increase the lifespan of wild-type *Drosophila* (Proshkina et al., 2016). Quercetin supplementation in mice did not cause beneficial effects on longevity (though this was only tested in combination with polyphenolic taxifolin and pycnogenol) (Spindler et al., 2013). However, in combination with the chemotherapeutic dasatinib, quercetin acted senolytically, thus removing senescent cells *in vivo*, and improved cardiac function of aged mice while overall promoting the healthspan (Zhu et al., 2015). Of note, genetic ablation of senescent cells by means of an inducible suicide gene can extend rodent lifespan up to 25% (Baker et al., 2016). However, the contribution of senescent cells to aging progression—although well explored—remains to be fully understood and incorporated into an applicable model (van Deursen, 2014). In fact, the concept of senolytic drugs has only recently been developed, and more extensive mechanistic studies are needed to strengthen and elaborate the idea. For instance, the above-mentioned studies suggesting quercetin (in combination with other agents) to be senolytic but to fail in extending lifespan (Spindler et al., 2013; Zhu et al., 2015) may reflect a greater contribution of senolytic activity to healthspan than to lifespan-extension. However, differences in the agents used for combinations, application, dosage, timing, and mouse strains among other factors in these two studies underline that further analyses are warranted to evaluate possible pro-longevity effects of quercetin.

Furthermore, *in vivo* anti-cancer and anti-inflammatory effects as well as improvements of insulin sensitivity and HFD-induced weight gain have been described for quercetin (Chen et al., 2016; D'Andrea, 2015). Only slow progress has been made in translating these results to clinical trials: ambiguous results of quercetin supplementation on inflammation were reported. Quercetin improved blood pressure in hypertension, obesity, and type 2 diabetes patients (D'Andrea, 2015), also reducing plasma levels of oxidized low-density lipoprotein (Egert et al., 2009). Although safe for human application, quercetin bioavailability is low and metabolization is high (D'Andrea, 2015), two features that might reduce its clinical utility.

The flavonoids (+)−catechin and its cis-form (−)−epicatechin can be prominently found in cocoa, tea brews, and red wine. Several animal studies and human trials have shown cardiovascular protective properties of catechins (Aprotosoaie et al., 2016). Both catechins reduce cytosolic protein acetylation and induce autophagy (Pietrocola et al., 2012), likely via pleiotropic targets. Epicatechin was suggested to act in a SIRT1-independent fashion (de Boer et al., 2006), and its dietary supplementation in wild-type flies and obese diabetic mice reduced mortality in both species and improved markers of systemic inflammation and diabetes-associated liver and aorta degeneration in the latter (Si et al., 2011). This is of special interest since epicatechin has been suggested as an insulin receptor activator by *in silico* analyses (Ganugapati et al., 2011). Catechin also improves stress resistance and extends the lifespan of nematodes, independently of antioxidative properties (Saul et al., 2011). The bioavailability of epicatechin appears favorable (Steffen et al., 2008) and numerous clinical trials have proven basic safety in patients. Epicatechin was shown to improve insulin resistance (Dower et al., 2015) and alter gene expression profiles, slightly downregulating inflammation- and adipogenesis-associated genes (Esser et al., 2018). Interestingly, epicatechin supplementation improved CVD markers and reduced triglyceride levels in patients with hypertriglyceridemia (Gutiérrez-Salmeán et al., 2016). However, many studies use chemically non-defined catechin-enriched (tea) extracts, rendering their evaluation problematic.

Epigallocatechin-3-gallate (EGCG) is the major polyphenol in green tea. It has numerous biological effects and pleiotropic molecular targets. Notably, it strongly inhibits HATs, activates SIRT1 (Lee et al., 2015a), and extends lifespan in worms (Abbas and Wink, 2009), flies (Wagner et al., 2015), and rats (Niu et al., 2013). It induces autophagy in cell culture in a reportedly Ca^{2+}/calmodulin-dependent protein kinase kinase beta (CaMKKβ)-dependent fashion (Kim et al., 2013) and inhibits EP300/CBP (Ko et al., 2013). However, the exact role of protein deacetylation in EGCG-mediated pro-autophagic effects remains unclear. Additionally, reduced glucose metabolism and increased fitness of flies (Wagner et al., 2015) were reported. In rodents, EGCG improved liver and kidney function and reduced NF-κB signaling (Niu et al., 2013). EGCG may stimulate AMPK, probably via the activation of the upstream kinase Ca^{2+}/calmodulin-dependent protein kinase kinase (CaMKK) (Collins et al., 2007). Several studies found promising effects of EGCG on the reduction of obesity and high-calorie-associated effects in rodents (Legeay et al., 2015). A 2013 study, however, did not find changes in metabolism, body weight, or liver function in nutritionally supplemented obese women (Mielgo-Ayuso et al., 2014). EGCG has also been suggested as a potential anti-cancer therapeutic (Du et al., 2012) and improves insulin sensitivity, glucose metabolism, and endothelial function in mice (Legeay et al., 2015). Prominently, EGCG was intensively studied in the context of neurodegeneration (including in clinical trials), as its anti-aggregation properties hold great promise (Cascella et al., 2017). Of note, a green tea extract (31.7 % EGCG, 8.5 % epicatechin) was neuroprotective and improved learning capacities in a

progeroid mouse model when fed lifelong or from adulthood (Unno et al., 2009). In humans, EGCG bioavailability is rather poor, challenging the utility of its clinical use (Legeay et al., 2015). Moreover, it has been reported that continuous intake of more than 800 mg per day may cause liver toxicity in patients (Hu et al., 2018). Finally, the alkaloid polyphenol berberine activates autophagy via SIRT1 and reduces protein acetylation (Shukla et al., 2016), protecting liver function (Sun et al., 2018), exerting neuroprotective effects (Wang et al., 2017), and reducing cardiac damage (Yu et al., 2016) in rodents. Berberine was also shown to extend the lifespan of *Drosophila* (Navrotskaya et al., 2012). Though oral bioavailability of berberine is poor (Liu et al., 2016), several clinical studies have been or are being performed with berberine supplementation. Noteworthy, berberine showed hypoglycemic effects and improved insulin parameters in type 2 diabetes patients (Yin et al., 2008).

In general, polyphenols represent a chemical group with a great potential to find pharmacological alternatives to CR. For instance, a recent study screening for pro-longevity drugs identified the flavonoid 4,4′-dimethoxychalcone as a pro-autophagic natural compound (present in the plant *Angelica keiskei*, also known as Ashitaba). 4,4′-Dimethoxychalcone can extend lifespan from yeast to flies and shows cardioprotective effects in mice, all in an autophagy-dependent manner (Carmona-Gutierrez et al., 2019).

It is important to note that most polyphenols possess antioxidant properties and have pleiotropic effects on several molecular targets, rendering it difficult to study their precise mode of action. Moreover, modifications such as glycosylation are likely to change their bioactive features *in vivo*. For instance, glycosylation greatly modulates the effects of quercetin on the worm lifespan and probably alters its bioavailability (Pallauf et al., 2017).

Metformin

Metformin (dimethylbiguanide hydrochloride) is a derivative of natural guanidines present in the French lilac (*Galega officinalis*), a plant that has been used in folk medicine for centuries. Originally described as a hypoglycemic and antimalarial drug, it is currently a widely prescribed agent in the treatment of type 2 diabetes. Interestingly, metformin administration extends the lifespan in different animal models, including mammals (Martin-Montalvo et al., 2013). In humans, metformin seems to be beneficial against a number of age-related diseases, including cancer and metabolic syndrome as well as cognitive and cardiovascular disorders (Foretz et al., 2014; Greenhill, 2015). Indeed, a recent meta-analysis of diabetics on metformin use has revealed that this drug reduces all-cause mortality and age-associated diseases (Campbell et al., 2017). This geroprotective potential paired with its little side effects has propelled the start of several clinical trials. Metformin recapitulates important metabolic effects of CR (Onken and Driscoll, 2010) and stimulates protective autophagy, for instance in mouse models of obesity and cardiac dysfunction (Li et al., 2017a; Xie et al., 2011).

Mechanistically, metformin has been associated with the activation of the master energy sensor AMPK (Duca et al., 2015) via the inhibition of the mitochondrial electron transport chain complex I (Owen et al., 2000), although it might activate AMPK through a lysosomal pathway, as well (Zhang et al., 2016b). In addition, metformin also inhibits mTORC1 independently of AMPK (Nair et al., 2014). Whether metformin effects rely on protein hypoacetylation remains to be systematically evaluated. In fact, metformin-mediated AMPK activation has been associated with both reduced EP300 and CREB-binding protein (He et al., 2009; Lim et al., 2012) and increased HAT (HAT1) activity (Marin et al., 2017). Similarly, metformin can inhibit class II HDACs (Khan and Jena, 2016) but can also stimulate class III HDAC SIRT1 activity, possibly downstream of AMPK activation (Caton et al., 2010). Metformin may also impact SIRT1 gene expression directly. Altogether the current data suggest that metformin could qualify as a *bona fide* CRM if causal effects on protein hypoacetylation were validated.

Rapamycin and Related Compounds (Rapalogs)

Rapamycin (sirolimus) is a macrolide compound produced by *Streptomyces hygroscopicus*. It was originally used as an antifungal drug and is an FDA-approved immunosuppressant that has been shown to extend lifespan in *C. elegans*, *D. Melanogaster*, and mice (Ehninger et al., 2014). Rapamycin has also been connected, for example, to cardioprotection (Chiao et al., 2016), anti-neurodegenerative effects (Kolosova et al., 2013), and obesity prevention (Chang et al., 2009) in rodents. Numerous clinical trials have addressed the efficacy of rapamycin and rapamycin analogs (rapalogs) in treating diseases, including cancers. Rapamycin can inhibit mTORC1 by forming a complex with the protein FKBP12 (Boutouja et al., 2019). As a specific mTORC1 inhibitor, rapamycin promotes autophagy independently of SIRT1 (Kim and Guan, 2015) but links to possible autophagy-relevant deacetylation processes have been documented (Füllgrabe et al., 2013). Whether such deacetylation processes contribute to the beneficial effects of rapamycin will clarify if it fully qualifies as a CRM. However, its immunosuppressant properties compromise the broad clinical application. In addition, prolonged rapamycin treatment exacerbates insulin resistance and diabetes (Lamming et al., 2012) and actually reduces the lifespan of diabetic mice (Sataranatarajan et al., 2016). Whether intermittent administration of rapamycin might circumvent these adverse effects needs further investigation.

Rapamycin belongs to the so-called first generation mTOR inhibitors, which also comprise the rapalogs temsirolimus and everolimus, both of which also bind FKB12 but show improved pharmacokinetics (Boutouja et al., 2019). While the first generation rapalogs and rapamycin only block mTORC1, the second generation of mTOR inhibitors (NVP-BEZ235, PF-04691502, OSI-027, and others) acts by blocking the ATP site of the mTOR kinase, thus also affecting TORC2 (Boutouja et al., 2019). A series of clinical trials for specific medical applications have been conducted or registered for some of these drugs, but further evaluation is required to assess whether they also possess health- and/or lifespan-extending features. Finally, the third generation of mTOR inhibitors includes bivalent drugs that target multiple molecular targets in the TOR complexes (e.g., mTOR kinase, FRB domain, and FKBP12), providing enhanced effectivity against, for instance, tumorous cells (Boutouja et al., 2019; Fan et al., 2017). One recent example of this category is RapaLink-1, which is a specific TOR kinase inhibitor linked to rapamycin (Fan et al., 2017). This generation, however, has not surfaced to clinical studies yet.

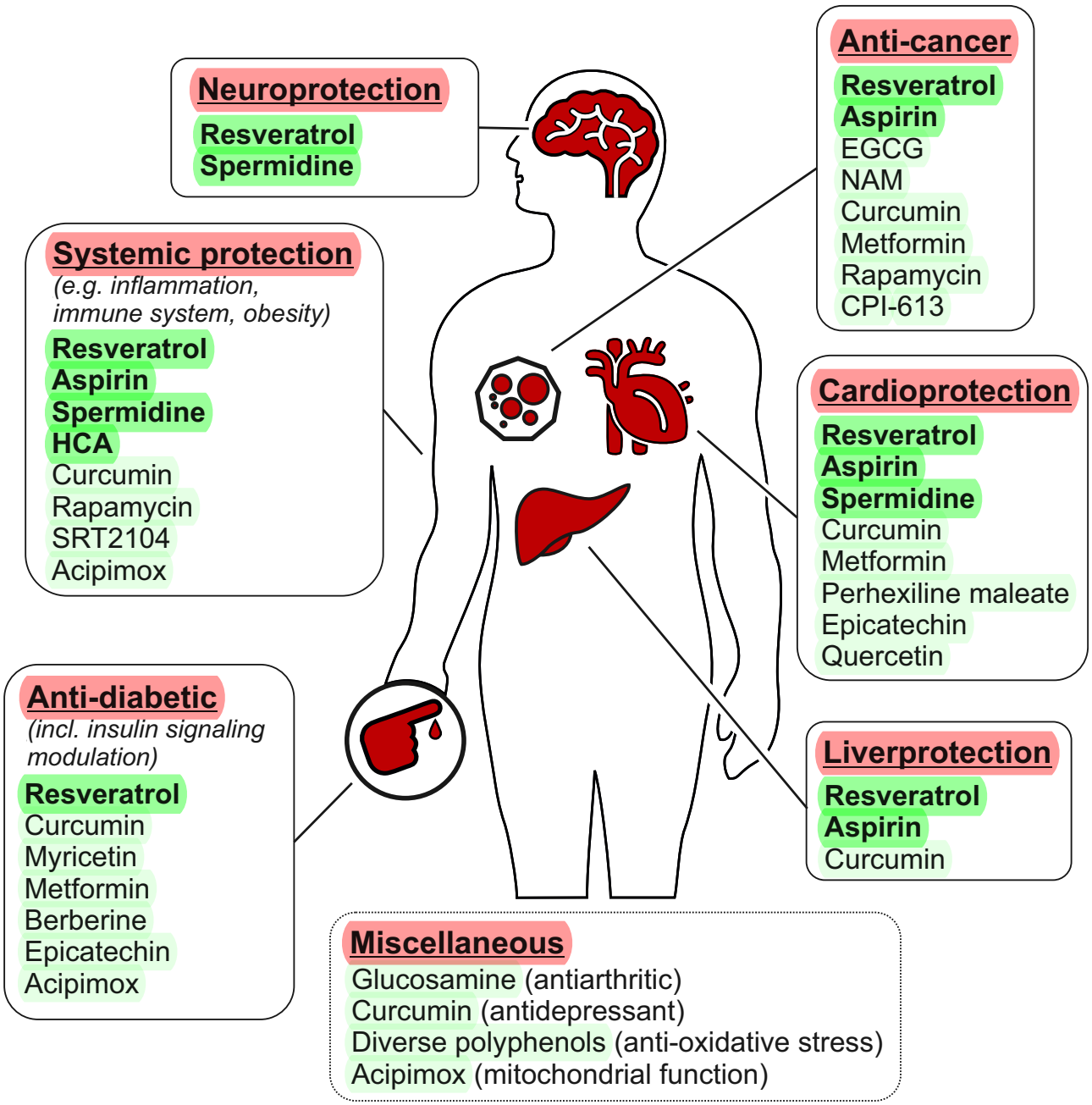

Figure 3. Possible Physiological Effects of CRMs Seen in Clinical Studies
CRMs positively affect human health both at the systemic and tissue-specific levels. Bold, CRMs; normal, potential CRMs. EGCG, Epigallocatechin-3-gallate; HCA, hydroxycitric acid; NMN, nicotinamide mononucleotide; NAM, nicotinamide.

Modulation of Glucose Metabolism

Blocking cellular energy utilization, specifically glycolysis, has been devised as a CRM strategy. Glucose deprivation alone is sufficient to induce autophagy via AMPK/mTOR (Moruno et al., 2012). The hexokinase inhibitor glucosamine is a widely used agent to prevent and treat osteoarthritis and shows no relevant side effects. In fact, glucosamine medication has been associated with decreased mortality in humans (Bell et al., 2012). Autophagy activation by glucosamine was proposed to be both mTOR dependent (Caramés et al., 2013) and independent (Shintani et al., 2010), meaning that the exact pathway is still debated. Whether protein deacetylation is involved in glucosamine-mediated autophagy induction remains to be studied. Instead, 2-deoxyglucose (a synthetic hexokinase 2 inhibitor) increases nematode lifespan but seems to be cardiotoxic and to increase mortality in rats (Minor et al., 2010). In line with the latter results, 2-deoxyglucose treatment suppresses autophagy via activation of mTORC1 (Roberts et al., 2014) and does not

Table 2. Effects of CRMs, Potential CRMs, and Other Compounds on Rodent Lifespan

Group	Substance	Organism	Lifespan Extension	Application Scheme	References
CRMs	aspirin (and salicylate)	mouse (male UM-HET3; failed in females)	~8% median lifespan increase	starting at 4 months; supplemented via Purina 5LG6 diet	Strong et al., 2008
	resveratrol	mouse (male C57BL/6NIA)	31% reduced risk of death	starting at 12 months; supplemented via diet; on high-calorie diet	Baur et al., 2006
	spermidine	mouse (male and female C57BL/6J)	~12% or ~10% median lifespan increases for lifelong or late-in-life supplementation, respectively	starting at 4 or 18 months; supplemented via drinking water; standard diet	Eisenberg et al., 2016
Potential CRMs	curcumin (or tetrahydrocurcumin)	mouse (male C57BL/6)	11.7% mean lifespan increase	starting at 13 months; supplemented via standard diet	Kitani et al., 2007
	epicatechin	mouse (db/db obese, diabetic model)	reduced mortality (8.4% in treated versus 50% in control group after 15 weeks of treatment)	starting at 5 weeks; supplemented via drinking water	Si et al., 2011
	EGCG	rat (male Wistar)	~13.5% median lifespan increase	starting at 5 weeks; supplemented via drinking water	Niu et al., 2013
	metformin	mouse (male C57BL/6 and B6C3F1)	5.83% (C57BL/6) and 4.15% (B6C3F1) mean lifespan increase for low dose (0.1%); high dose (1%) led to 14.4% mean lifespan reduction	starting at 54 weeks; supplemented via standard diet	Martin-Montalvo et al., 2013
	NR	mouse (C57BL/6J)	~5% mean lifespan increase	starting at 22–24 months; via diet; for 6 weeks; standard diet	Zhang et al., 2016c
	rapamycin	mouse (male and female C57BL/6, UM-HET3, 129/sv)	median (~25%) and maximum lifespan increase (Miller et al., 2014); 10% median lifespan increase (Anisimov et al., 2011); median lifespan increase of 10% (males) and 18% (females) (Miller et al., 2011); mean lifespan increase of 9% (male) and 13% (female) (Harrison et al., 2009)	many different application methods and starting timepoints of intervention reported	reviewed in Ehninger et al., 2014
	SRT1720	mouse (male C57BL/6J)	11% and 44% mean lifespan increase for low and high doses	starting at 12 months; supplemented via diet; on high-fat diet	Minor et al., 2011
Others	CAPE	mouse (male and female $SOD1^{G93A}$ ALS model with B6SJL background)	~7% lifespan increase	single daily oral dose after disease onset	Fontanilla et al., 2012
	SRT2104	mouse (male C57BL/6J)	9.7% mean lifespan increase	starting at 6 months; supplemented via diet; on standard diet	Mercken et al., 2014

Lifespan experiments that have been performed in rodents with compounds listed in Table 1. Animal specificities (including sex), quantitation of lifespan improvement, experimental design for compound administration, and corresponding references are noted. CAPE, caffeic acid phenyl ester; EGCG, epigallocatechin-3-gallate; NR, nicotinamide riboside.

represent a CRM. Acarbose is an α-glucosidase inhibitor of bacterial origin (*Streptomyces* and *Actinoplanes* species) and widely used as an anti-diabetic medication, preventing the release of glucose from more complex carbohydrates (Brewer et al., 2016). Although it might be connected to further lifespan-determining effects (Harrison et al., 2014), additional studies that address its possible influence on autophagy and protein deacetylation are needed.

Conclusion

Ongoing and future clinical trials, as well as meta-analyses, will ultimately determine the actual beneficial impact of each CRM on human health (Figure 3). Further CRMs may be discovered and optimized versions of known CRMs obtained by medicinal chemistry that will need to be further evaluated. Besides, it will be important to tackle certain limitations (e.g., bioavailability) and unfold possibilities, including the prospect for combinatorial approaches. Many CRMs fail to extend lifespan to the same degree as CR or fasting does and some CRMs show sex-specific differences (Table 2), suggesting that CR might cumulatively ignite distinct pathways that are only partly targeted by single CRMs. This propels the idea of achieving additive effects by compound/treatment combinations. This applies to (1) combinations of distinct CRMs, (2) combinations of CRMs with other beneficial non-CRM compounds, and (3) combinations of CRMs with behavioral/nutritional approaches (e.g., fasting, CR, and exercise). With respect to (1), it can be expected that CRMs that act on distinct routes to achieve protein deacetylation (namely AcCoA depletion, acetyltransferase inhibition, or deacetylase activation) could interact in a synergistic fashion. For example, resveratrol (which promotes SIRT deacetylase activity) synergizes with spermidine (which is an acetyltransferase inhibitor) to promote autophagy *in vitro* (human cell culture) and *in vivo* (mice) (Morselli et al., 2011). Moreover, rapamycin and metformin act synergistically on worm lifespan (Admasu et al., 2018). These studies exemplify the substantial potential of such combinatorial approaches in the anti-aging field. Regarding (2), several health-promoting compounds including antioxidant and hormesis mimetics do not rely on the deacetylation-autophagy axis. It will be interesting to investigate whether they might be favorably combined with CRMs. Finally, (3) exercise, CR, fasting, and CRMs all promote autophagy, and additive or synergistic effects might be attained upon combining these interventions. For instance, several studies suggest that exercise might be combined with the CRM resveratrol (Liao et al., 2017).

Another important aspect is the timing of CRM application. First, the effective administration of CRMs in a middle-life stage (instead of lifelong application), before adverse age-associated symptoms manifest, would greatly enhance the therapeutic feasibility of CRMs for humans. Thus, exploring whether specific CRMs can be effective also upon administration late in life will help clarify the extended potential of these drugs. Second, the application of CRMs in a rhythmic fashion could reduce the drug load while promoting the same effects. This follows the idea that in humans, rhythmic variations of calorie intake (e.g., intermittent fasting) stimulate many of the favorable effects that constant CR does (Di Francesco et al., 2018). In fact, in animal and human studies, the timing of meals regarding the circadian clock is of utmost importance (Di Francesco et al., 2018). Third, the target availability for different CRMs might be optimized by timing the administration of a given CRM with the expression patterns of its corresponding target(s). In fact, if a specific cellular target is not expressed at relevant levels, a drug dose at this time point might be ineffective. Mechanistic data on cellular targets of specific CRMs are already available and solid. The experiments exploring "target expression-enhanced" administration might be especially interesting regarding variable expression profiles in different tissue types as well as with ongoing age and at a particular disease status.

Irrespective of the pending therapeutic validation of CRMs as a stand-alone and/or combinatory approach and other open questions, the available data substantiate the large potential of pharmacological autophagy induction as a feasible and effective strategy against multiple diseases.

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AUTHOR CONTRIBUTIONS

F.M., D.C.-G., S.J.H., and G.K. contributed to the conceptualization, figure design, and writing of the manuscript.

DECLARATION OF INTERESTS

G.K. is inventor on a patent application (WO2015049365 A3) submitted by INSERM (Institut National de la Santé et de la Recherche Médicale), Assistance Publique-Hôpitaux De Paris (APHP), Université Paris Descartes, Université Pierre et Marie Curie (Paris 6), Université Paris Diderot–Paris 7, Université Paris–Sud, Institut Gustave Roussy, that covers the medical use of CRMs. F.M. and D.C.-G. have equity interests in TLL (The Longevity Labs), a company founded in 2016 that will develop natural food extracts. F.M., D.C.-G., and G.K. are the scientific co-founders of Samsara Therapeutics.

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