Chapter 13
Health Benefits of Anti-aging Drugs

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Abstract Aging, as a physiological process mediated by numerous regulatory pathways and transcription factors, is manifested by continuous progressive functional decline and increasing risk of chronic diseases. There is an increasing interest to identify pharmacological agents for treatment and prevention of age-related disease in humans. Animal models play an important role in identification and testing of anti-aging compounds; this step is crucial before the drug will enter human clinical trial or will be introduced to human medicine. One of the main goals of animal studies is better understanding of mechanistic targets, therapeutic implications and side-effects of the drug, which may be later translated into humans. In this chapter, we summarized the effects of different drugs reported to extend the lifespan in model organisms from round worms to rodents. Resveratrol, rapamycin, metformin and aspirin, showing effectiveness in model organism life- and healthspan extension mainly target the master regulators of aging such as mTOR, FOXO and PGC1α, affecting autophagy, inflammation and oxidative stress. In humans, these drugs were demonstrated to reduce inflammation, prevent CVD, and slow down the functional decline in certain organs. Additionally, potential anti-aging pharmacologic agents inhibit cancerogenesis, interfering with certain aspects of cell metabolism, proliferation, angioneogenesis and apoptosis.

Keywords Aging · Lifespan · Healthspan · Model organisms · Anti-aging drugs

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J. R. Harris, V. I. Korolchuk (eds.), *Biochemistry and Cell Biology of Ageing: Part II Clinical Science*, Subcellular Biochemistry 91,
https://doi.org/10.1007/978-981-13-3681-2_13

Introduction

During the last few centuries, advances in medicine and pharmacology allowed mankind to substantially increase human lifespan. Dramatic increase in the proportion of individuals >60 years is observed worldwide – from 9.2% in 1990 to 11.7% in 2013, with expected 21.1% (>2 billion) in 2050 (Sander et al. 2015). However, age-related disease prevalence and costs, associated with cardiovascular diseases, cancer, type 2 diabetes mellitus, cognitive impairment and dementia in elderly are overwhelming for many well-developed healthcare systems. Elderly patients are often experiencing an everyday struggle with multiple chronic conditions and disability. All of the above mentioned shifts focus on healthspan/quality of life prolongation, not just life extension (Hansen and Kennedy 2016). Non-pharmacological approaches to delay age-related decline including diet and physical activity have been extensively studied and have proved to provide some life-extending and disease-preventing benefits (Di Daniele et al. 2017; McPhee et al. 2016). Strategies of life- and healthspan extension with administration of drugs and their combinations remain tempting. Recent research, concentrated on prolonging life of model organisms and humans, is mainly focused on well-known pharmacological agents, as well as food-derived substances (Vaiserman et al. 2016; Vaiserman and Lushchak 2017a). Some of the FDA-approved substances target one or several mechanisms, associated with age-related cellular and molecular dysfunctions. Aspirin, statins, rapalogs, metformin, as well as lisinopril, propranolol, caloric restriction and exercise target compounds contributing the same age-related cellular dysfunction, known as senescence-associated secretory phenotype (SASP). SASP seems to be a hallmark of age-related diseases, being a cause of functional decline (Blagosklonny 2017). Each of the above mentioned agents blocks different parts of the mechanism contributing to dysfunction and further organ damage. However, a large part of the mechanisms mediating the anti-aging properties of medications remain essentially unknown (Vaiserman and Lushchak 2017b). In the present chapter, molecular targets and the anti-aging effects of aspirin, statins, metformin and rapamycin will be described. We will look into data obtained in different model organisms and assess the evidence obtained in clinical trials, addressing gaps, restrictions and limitations of current research.

Anti-aging pharmacology seems to be an extremely promising and challenging field, facing multiple constrains in different aspects. A lack of tangible, measurable, biomarkers of human aging appears to be one of the cornerstone issues. Surrogate endpoints, like cardiovascular disease or cognitive impairment or mortality are used in clinical trials, thus the introduction of alternative, easily measurable biomarkers with high predictive value is of extreme importance. The same problem affects biomarkers applied to animal models; it remains unclear whether these might be efficiently translated into human medicine. Many side effects, potentially occurring in humans cannot be evaluated in model organisms. Further investigation on optimal beginning of drug exposure need to be conducted, while some medications might have a certain therapeutic window of effect, when drug exposure is the most beneficial. The question of dosing also remains unsolved, while some of the actions

seem to have a dose-dependent effect, strongly varying in dependence on individual metabolizing activity (Burd et al. 2016).

Some of the drugs might undergo repurposing, like aspirin, have emerged over the course of the last century, and further attempts are being made to introduce aspirin and metformin as adjuvant anti-cancer treatments and/or cancer prevention medication (Yue et al. 2014).

Food-derived substances with evidence for prolonging lifespan and preventing age-related functional decline and disease, represent an expanding research area with promising perspectives for development of new preventive and/or treatment strategies. Difficulties in this field include absent recommended daily allowance for humans, extremely high variability in content of these substances in different products, depending on the area of cultivation, type of processing etc. Furthermore, many of the antioxidant substances have failed to demonstrate benefits in life extension or disease prevention when tested in model organisms. Perhaps, the synergetic effects of multiple whole food compounds remain underestimated by researchers. Many reviews concentrate on the idea that targeting reactive oxygen species as primary aging-driving mechanism is wrong (Gruber and Halliwell 2017).

Lifespan Extension in Model Organisms

Aging is the physiological process that is characterized by the loss of normal organ function caused by damage accumulation in cells and tissues (Fontana et al. 2007). Longevity can be modulated by alterations in age-related genes. Moreover, lifespan might be extended using some drugs. Discovery of chemicals that can delay aging and extend lifespan is one of the most promising potential ways to improve the quality of life in older age. Today, many of the prolongevity drugs are effective at relatively low concentrations from 5 to 200 mg/kg of body weight (Hayashi and McMahon 2002). However, it is important to know that every compound may possess some side effects. Furthermore, many drugs may extend lifespan by so called hormetic effect: i.e. the conditions, where relatively toxic substances may have beneficial effects.

There is a continuous need of optimal model system to discover potential anti-aging properties and evaluate the effect on healthspan. Ideally, model system should maximally replicate ageing processes in humans, including genes and signaling pathways that exhibit high conservation. More often the researchers use simple model organisms such as nematodes, fruit flies and rodents. Most studies aimed to investigate the anti-ageing drugs were performed by using invertebrate models, which are considered as useful models for human disease exploration and are widely used for discovering potential anti-ageing agents (Markaki and Tavernarakis 2010; Millburn et al. 2016; Ugur et al. 2016). Pathways controlling lifespan and aging are partially conserved in a wide range of species, from yeast to humans (Bitto et al. 2015; Fontana et al. 2010). In this part, we collected and summarized data obtained in invertebrate and rodent models indicating the anti-aging potential medicines. Aspirin, rapamycin, resveratrol and metformin were effective to extend the lifespan

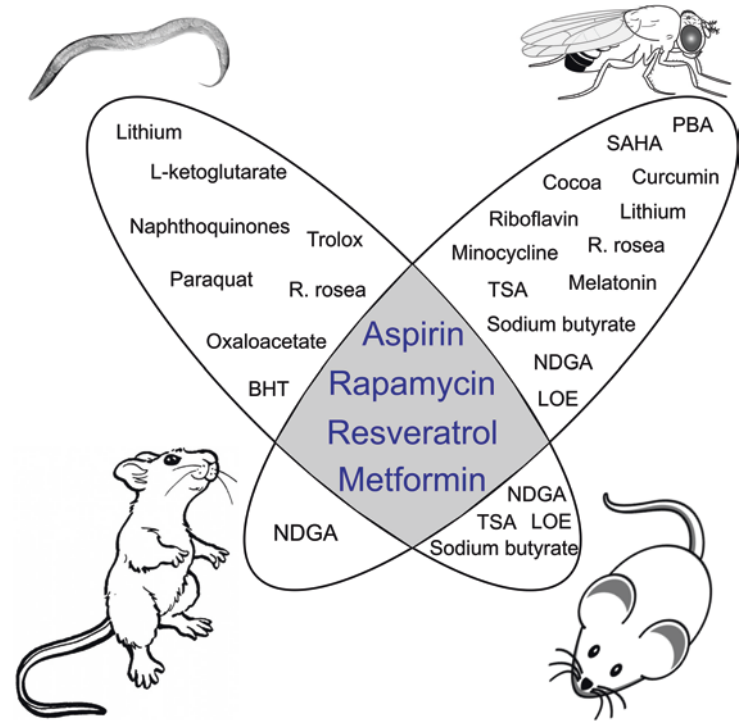

Fig. 13.1 Pharmaceuticals with lifespan-extending properties in different animal models. Drugs extending lifespan of nematode *C. elegans* belong to antioxidants, metabolites, natural compounds, kinase inhibitors. Many agents were shown to extend the lifespan in fruit fly *D. melanogaster*. Some drugs have significant effects on healthspan in several rodent models, however direct effects on lifespan were not demonstrated. Commonly used drugs, including aspirin, rapamycin, resveratrol and metformin, have been found to delay aging and improve overall health in all discussed animal models. *PBA* phenylbutyrate, *BHT* D-β-hydroxybutyrate, *SAHA* suberoylanilide hydroxamic acid, *TSA* Trichostatin A, *NDGA* nordihydroguaiaretic acid, *LOE Ludwigia octovalvis* extract

in four model organisms. Many more drugs, such as Trichostatin A (TSA), sodium butyrate, lithium, Nordihydroguaiaretic acid (NDGA) as well as plant extracts from *Rhodiola rosea* or *Ludwigia octovalvis* have extended the lifespan in more than one model (Fig. 13.1).

Round Worm *Caenorhabditis elegans*

To date, many drugs extending nematode *C. elegans* lifespan have been discovered. They mostly belong to antioxidants, metabolites, natural compounds and kinase inhibitors. Interestingly, these compounds affect the signaling pathways involved in

lifespan regulation. Similar mechanisms involved in modulation of lifespan in nematodes and mammals were shown for aspirin, rapamycin, metformin, resveratrol (Fig. 13.1). Thus, this worm is an excellent model system to test prolongevity properties of pharmacological interventions. Besides short lifespan, small size and amenability to genetic manipulations, many genetic pathways affecting aging are conserved in *C. elegans*.

Antioxidants are the most studied class of anti-aging compound (Harman 1972; Melov et al. 2000). Vitamin E (tocopherol) was shown to extend *C. elegans* lifespan (Harrington and Harley 1988; Ishii et al. 2004). Moreover, the α-tocopherol derivative trolox also demonstrated a positive effect on nematode survival (Benedetti et al. 2008). These results support the oxidative damage theory, with the central concept of molecular damage caused by reactive oxygen species (ROS) affect aging (Harman 1956). Interestingly, there are also some controversial results, which revealed lifespan shortening effect under EUK-8 and EUK-134 supplementation (Kim et al. 2008). However, vitamin C, which is the most powerful antioxidant, had no effect on nematode lifespan (Harrington and Harley 1988). The theory of hormesis claims that low doses of stressful agents activate a stress response and as a result improved longevity. Indeed, ROS generating compounds such as naphthoquinones extend nematode lifespan (Hunt et al. 2011). Furthermore, administration of low doses of paraquat or rotenone increased the lifespan in *C. elegans* (Lee et al. 2010a, b) (Figs. 13.2 and 13.3).

Aging is strongly affected by metabolism. Besides dietary restriction, some pharmacological perturbation of metabolism showed beneficial effects on longevity. Several studies have demonstrated increased nematode lifespan by metabolic intermediates. Williams and colleagues showed that oxaloacetate supplementation

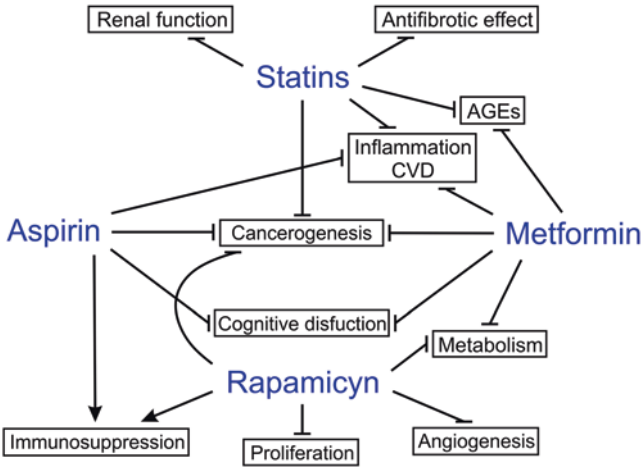

Fig. 13.2 Aging-associated processes affected by statins, aspirin, metformin and rapamycin. Schematic representation of the main physiological processes and diseases targeted by life-extending drugs. *CVD* cardiovascular disease, *AGEs* advanced glycation end-products

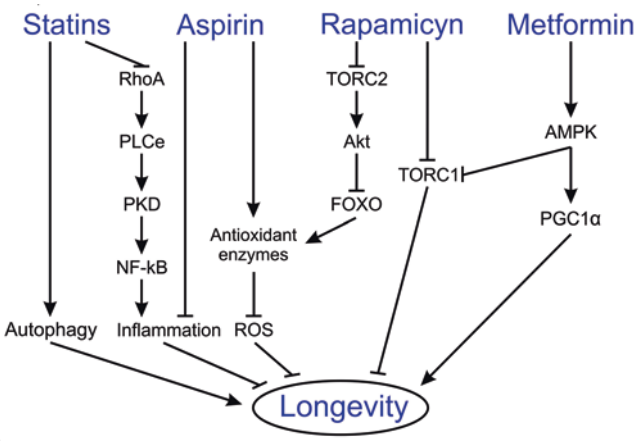

Fig. 13.3 Signaling pathways and mechanisms mediating the lifespan-extending effects of drugs. An association between autophagy induction and lifespan extension has been revealed in various experimental models. Both statins and aspirin decrease inflammation. The ability of aspirin and rapamycin to regulate expression of genes encoding antioxidant enzymes was elicited. Rapamycin inhibits TORC1 that regulates longevity by phosphorylation of 4EBP and S6K. Metformin acts via AMPK-activator to inhibit TORC1 or activate PGC1α. *RhoA* Ras homolog gene family member A, *PLCe* Phospholipase C Epsilon, *PKD* protein kinase D, *NF-kB* nuclear factor k-light-chain-enhancer of activated B cells, *ROS* reactive oxygen species, *TORC1/2* target of rapamycin complex 1/2, *Akt* Protein kinase B, *FOXO* Forkhead box protein O, *AMPK* AMP-activated protein kinase, *PGC1α* Peroxisome proliferator-activated receptor γ coactivator 1α

extended lifespan of *C. elegans* (Williams et al. 2009). Also, α-ketoglutarate, a tricarboxylic acid cycle intermediate, extended the lifespan of adult *C. elegans* (Chin et al. 2014). Furthermore, α-ketoglutarate as a key metabolite of TCA, acts as a messenger of dietary restriction in aging control. Interestingly, α-ketoglutarate affects the nematode lifespan through inhibiting the TOR signaling pathway (Chin et al. 2014). Malate, as a TCA metabolite, increased lifespan and thermotolerance in *C. elegans*. Additionally, fumarate and succinate also extend nematode lifespan. These compounds realized their effect through the activation of conserved stress response pathways.

Metabolomic analysis demonstrated increased content of glutamine, valine, and isoleucine in long-lived daf-2 mutant worms (Edwards et al. 2015). This suggested that amino acid food supplementation can slightly extend nematode lifespan. Moreover, a lifespan extension effect under histidine and tryptophan was accompanied with endoplasmic reticulum (ER) stress response activation; proline and tryptophan increase thermotolerance; tryptophan supplementation increases proteotoxicity (Edwards et al. 2015).

Metformin is widely known for its anti-hyperglycemic properties and thus used for type 2 diabetes (T2D) treatment. The effect of metformin treatment on *C. elegans* aging was investigated by Onken and Driscoll (2010). This study demonstrated improved nematode healthspan, locomotor activity and median lifespan under metformin administration. Interestingly, this biguanide acts in a dietary restriction man-

ner and activates an oxidative stress response. Furthermore, it affects lifespan via AMPK, LKB1, and SKN-1 but is independent of insulin signaling (Onken and Driscoll 2010). Metformin also mediates DR and oxidative stress pathways in a lifespan extending effect. Hence, metfomin may be a promising pharmacological intervention, with a complex beneficial impact on physiology.

Many kinase inhibitors are known to extend *C. elegans* lifespan, including rapamycin (Ye et al. 2014). A life-extending effect of rapamycin was shown in a number of studies from yeast to mammals. It is known that rapamycin realize its action through inhibiting the target of rapamycin (TOR) signaling pathway. TOR is essential for growth processes and is associated with disease and aging. Rapamycin triggers TOR inhibition which in turn leads to activation protective genes by SKN-1/Nrf and DAF-16/FoxO, and it enhances stress resistance and longevity (Robida-Stubbs et al. 2012). TOR inhibition or rapamycin treatment promotes longevity at least in part by reducing mRNA translation (Bjedov et al. 2010; Kapahi et al. 2010; Zid et al. 2009).

Potent cyclooxygenase-2 (COX-2) inhibitor, celecoxib extends *C. elegans* lifespan and delays the age-associated physiological changes, such as decline of locomotor activity (Ching et al. 2011). Celecoxib as a nonsteroidal drug is often used to treat pain and inflammation. The lifespan extension by celecoxib depends on the activity of DAF-16, the FOXO transcription factor known to regulate development and longevity downstream of insulin signaling (Lin et al. 1997; Ching et al. 2011). It was suggested that celecoxib might extend lifespan by inhibiting the kinase activity of 3-phosphoinositide-dependent kinase-1 (PDK-1) (Ching et al. 2011). Furthermore, celecoxib extends the lifespan of animals with reduced food uptake and mitochondrial respiration (Ching et al. 2011).

A *C. elegans* lifespan extension effect was also shown for histone deacylase (HDAC) inhibitors (Pasyukova and Vaiserman 2017). Ketone body D-beta-hydroxybutyrate (D-βHB), an endogenous and specific inhibitor of class I HDACs, has important implications for the pathogenesis and treatment of metabolic, neurodegenerative, and other aging-related pathological conditions (Edwards et al. 2014; Newman and Verdin 2014). In addition, the supplementation with D-βHB enhanced thermotolerance, prevented glucose toxicity, decreased α-synuclein aggregation (a sign of Parkinson's disease) and delayed amyloid β toxicity (a sign of Alzheimer's disease). Lithium is frequently used for bipolar disorder treatment; it also extend *C. elegans* lifespan via an epigenetic mechanism by altering expression of genes encoding nucleosome-associated functions (McColl et al. 2008). Longevity caused by lithium treatment is achieved by modulating histone methylation and chromatin structure.

Aspirin was found to have many beneficial effects on physiological traits and is often used to treat pain and inflammation. Aspirin treatment extended the nematode lifespan and improved stress resistance (Wan et al. 2013; Ayyadevara et al. 2013). Data also suggest that aspirin may act in a DR-like manner (Wan et al. 2013). Furthermore, it attenuates ROS amounts by triggering the expression of genes encoding antioxidant enzymes, such as catalase, superoxide dismutase and glutatione-*S*-transferase (Ayyadevara et al. 2013).

Numerous natural compounds including blueberry polyphenols, curcumin, quercetin, *ginkgo biloba* extracts, and resveratrol were shown to extend *C. elegans* lifespan and increase resistance to various stresses (Wu et al. 2002; Wilson et al. 2006; Pietsch et al. 2009). The plant polyphenol resveratrol is well characterized natural compound with annotated lifespan-extending properties. Lifespan extension by resveratrol is associated with NAD^+-dependent histone deacetylase, SIR-2.1 (Bass et al. 2007). The effect of resveratrol on lifespan in *C. elegans* could indicate induction of phase 2 drug detoxification or activation of AMP kinase (Bass et al. 2007). Interestingly, resveratrol did not extend nematode lifespan under normal condition, but induced longevity phenotype under condition of oxidative stress (Chen et al. 2013). *Rhodiola rosea* extract was also found as a promising anti-aging remedy. The lifespan-extending effect was observed in nematodes treated with *R. rosea* extract (Wiegant et al. 2009). This effect was associated with increased stress resistance. The suggested molecular mechanism of *R. rosea* is hormesis (Wiegant et al. 2009), due to the toxic effect at high doses that causes additional stress (Mattson 2008).

Some antidepressants showed positive effects on nematode longevity (Rangaraju et al. 2015). The atypical antidepressant, mianserin, induced oxidative stress resistance and extended *C. elegans* lifespan, but typical antidepressant fluoxetine had no impact on nematode physiology (Rangaraju et al. 2015).

Conclusively, drugs and compounds of different classes and origins were shown to extend the lifespan of worms evolving different pathways and mechanisms. However, there is a need to confirm the effects on other model organisms.

The Fruit Fly *Drosophila melanogaster*

Invertebrate model systems, including *Drosophila melanogaster*, are essential for better understanding the genetic pathways that control aging. Furthermore, the fruit fly is proved to be valuable in testing chemical compounds that may influence longevity. The *Drosophila* model is characterized by the existence of complex behavioral phenotypes and availability of several models of human age-related diseases. Furthermore, *Drosophila* experiments might be conducted in demographic cages, which allow one to take into account any bio-demographic effect on lifespan.

Numerous studies describe the effect of antioxidant dietary supplementation on *Drosophila* longevity. It was shown that an increased median and maximum fly lifespan could be induced by the antioxidant and glutathione precursor N-acetylcysteine (Brack et al. 1997). Vitamin supplementation with known antioxidants, also has lifespan extending effects. Vitamin E or α-tocopherol, was found to suppress several phenotypes in *Drosophila* models of neurodegenerative diseases like taupathies (Dias-Santagata et al. 2007), Parkinson disease (Wang et al. 2006), or pantothenate-kinase-associated neurodegeneration (Yang et al. 2005). Vitamin E extends lifespan of flies with deficiencies in oxidative stress response such as hyperoxia or in Cu/Zn superoxide dismutase-deficient (SOD1-deficient) flies under normoxia (Bahadorani et al. 2008). An extended lifespan increased

reproduction and catalase activity, with decreasing level of lipofuscin level shown under riboflavin supplementation. It acts via pathways related to oxidative stress (Zou et al. 2017). The lifespan-extending effect of melatonin was found to prevent oxidative damage to the fly tissues and slow down aging (Bonilla et al. 2002). The optimal dosage of NDGA (nordihydroguaiaretic acid) shown to extend the lifespan of flies was 100 μg/ml (Miquel et al. 1982).

Protein homeostasis plays an important role in aging and age-related pathologies. Curcumin prevents protein aggregation and increases lifespan in *D. melanogaster*. Its effects are associated with enhanced stress resistance (Lee et al. 2010a, b) by increased superoxide dismutase activity (Suckow and Suckow 2006; Shen et al. 2013). It was demonstrated, that curcumin acts as scavenger for the superoxide anion, hydroxyl radical (at high concentration) and nitric oxide (Kunchandy and Rao 1990; Brouet and Ohshima 1995).

Beneficial effects of lithium suggest its use for treatment of age-related diseases, mostly by hermetic mechanisms. Therapeutic concentration of lithium for mood disorders is close to the toxic doses (Lucanic et al. 2013). Lithium in low-doses extended fly lifespan by inhibition of glycogen synthase kinase-3 (GSK-3) and activation of the transcription factor nuclear factor erythroid 2-related factor (NRF-2) (Castillo-Quan et al. 2016). Higher doses of the drug, however, were found to reduce the lifespan.

Inhibitors of the histone deacetylases (HDACs) have been proposed as a promising type of therapeutic drugs able to modulate aging (Pasyukova and Vaiserman 2017). A lifespan extending effect in *Drosophila* was shown for 4-phenylbutyrate (PBA) treatment (Kang et al. 2002). PBA acts by histone (de)acetylation, a primary mechanism of epigenetic regulation (Vaiserman 2011). The effect of PBA is accompanied by changes in the acetylation level of histones H3 and H4 and transcriptional changes in significant set of genes (Pasyukova and Vaiserman 2017). Also, lifespan extending effects were shown for sodium butyrate (Zhao et al. 2005; McDonald et al. 2013; Vaiserman et al. 2013a, b) with annotated HDAC inhibition activity and shown to influence the processes of cell growth, differentiation and apoptosis (Buommino et al. 2000; Khan and Jena 2014). An increase of median and maximum *Drosophila* lifespan was observed when food was supplemented with Trichostatin A (TSA) (Tao et al. 2004; Zhao et al. 2005). This effect is characterized by induction of terminal differentiation, cell cycle arrest and also apoptosis in various cancer cell lines, thereby inhibiting tumorogenesis. The longevity phenotype induced by TSA is associated with the improvement of the cell stress resistance and locomotor activity. Suberoylanilide hydroxamic acid (SAHA) treatment resulted in a decreased mortality rate and extended longevity (McDonald et al. 2013). All these compounds affect several pathways involved in the regulation of gene expression patterns associated with healthy aging.

In general, the aging process is associated with inflammation. Non-steroidal anti-inflammatory drugs extended the lifespan in various model organisms, with demonstrated anticancer effects, tumor suppression and apoptosis stimulation (Poole et al. 2004; Danilov et al. 2015). Furthermore, NSAIDs increase locomotor activity and stress resistance in *Drosophila*. Interestingly, they have both anti- and pro-oxidant

properties, dependent on concentration (Danilov et al. 2015). Antioxidant properties are realized by their radical scavenging activity and membrane-stabilizing action (Danilov et al. 2015).

Aspirin was found to suppress aging process by interfering with oxidant production, cytokine response processes, and by blocking glycooxidation reactions (Phillips and Leeuwenburgh 2004). Prolonged *Drosophila* lifespan and improved healthspan was observed following aspirin administration (Song et al. 2017). The molecular mechanism of aspirin action still remains to be determined, but it influences the metabolism of amino acids, carbohydrates and urea.

The ability of resveratrol to extend the lifespan is conserved from yeast to mammals. Resveratrol treatment at a concentration of 400 μM was shown to extend mean lifespan in *Drosophila* when fed high-fat diet (Wang et al. 2013). Fly prolongevity phenotype was associated with downregulation of genes in aging-related pathways, including antioxidant peroxiredoxins and insulin-like peptides (Wang et al. 2013). As in worms, the lifespan extension was related to NAD^+-dependent histone deacetylase, Sir2 in *Drosophila* (Bass et al. 2007).

The antibiotic minocycline with anti-inflammatory, antioxidant and neuroprotective properties increases *Drosophila* survival and improves overall healthspan (Oxenkrug et al. 2012). Minocycline, as a key metabolite in the formation of kynurenine from tryptophan (KYN-TRP metabolism), is a promising candidate drug for delaying aging and treatment of aging-associated disorders.

TOR inhibition delays the aging process and increases lifespan in fruit flies (Kapahi et al. 2004; Luong et al. 2006). It was demonstrated that rapamycin causes a longevity phenotype via TOR inhibition, which in turn, modulates autophagy and translation. Increased resistance to starvation and paraquat treatment is accompanied by the lifespan-extending effect by rapamycin (Bjedov et al. 2010). Interestingly, rapamycin also reduces fecundity and increases lipid level in the fly body (Bjedov et al. 2010). The analysis of the rapamycin treatment under dietary restriction revealed slightly extended lifespan that had already been maximized by DR (Bjedov et al. 2010). The potential mechanism of rapamycin action is associated with its anticancer effects (Blagosklonny 2012a, b), induction of autophagy (Perluigi et al. 2015), anti-inflammatory effect (Araki et al. 2011).

Pharmacological interventions that mimic the effects of DR delay the onset of several age-related diseases in laboratory animals. A lifespan extending effect of metformin treatment in *C. elegans* was previously claimed (Onken and Driscoll 2010). However, it did not increase lifespan in either male or female flies (Slack et al. 2012). Moreover, higher metformin doses can be toxic to flies. Interestingly, metformin acts via AMPK to decrease body lipid stores (Slack et al. 2012).

R. rosea root extract as a promising anti-aging natural compound has been extensively used to protect against stress and to improve overall healthspan. The controversial studies showed that lifespan extension by *R. rosea* is independent (Schriner et al. 2013) or dependent of dietary composition (Gospodaryov et al. 2013). It delays age-related decline of physical activity and increases stress resistance. The mechanism of *R. rosea* action is still unknown, but it was demonstrated that it acts independently from TOR, IS and SIR2 (Schriner et al. 2013).

Cocoa, as a natural anti-aging compound, derived from *Theobroma cacao* increased lifespan in *D. melanogaster* and demonstrated antioxidant properties (Bahadorani and Hilliker 2008). Cocoa acts as an antioxidant under hyperoxia or during Cu/Zn-superoxide dismutase-deficiency (Bahadorani and Hilliker 2008). Moreover, it is involved in a heavy metal chelation process but may act as a pro-oxidant, when the level of oxidative stress is extremely high (Bahadorani and Hilliker 2008).

Rosemary (*Rosmarinus officinalis L.*) is known for its powerful antioxidant activity, antibacterial and hepatoprotective properties. Rosemary extract causes longevity phenotype in *Drosophila*, that is associated with increased superoxide dismutase and catalase activities (Wang et al. 2017a, b). *Ludwigia octovalvis* (LOE) is a rich source of antioxidants, including polyphenol compounds, phytosterols and squalene, extended lifespan of fruit fly fed regular or high-calorie diet (Lin et al. 2014; Wang et al. 2015). LOE attenuated age-related cognitive decline in fruit flies (Lin et al. 2014) and was shown to have anti-bacterial and anti-cancer activities (Chang et al. 2004).

Testing drugs with anti-aging properties, using *Drosophila* as a model system, is one of the most promising ways to understand the pharmacology of aging and lifespan extension. Rodent aging pharmaceuticals identification is the next step to investigate promising anti-aging therapies for humans.

The House Mouse *Mus musculus*

Mice have become a favorite model system for testing interventions in aging. The numerous of mouse advantages include short generation time, genetic proximity to humans (99% of human genes have their homologues in mouse), availability of strains and relatively small size. Mouse age-related models ensure a comprehensive tool for pharmaceutic compounds to affect longevity and genes implicated in the effects, to provide important general information about the genetic basis of ageing.

Beneficial effects of antioxidant supplements seem certain, however, lifespan extension were generally not described. Indeed, it was demonstrated that vitamin E is effective in suppressing phenotypes found in mouse models of human tauopathy (Nakashima et al. 2004) or Down syndrome (Lockrow et al. 2009). Furthermore, it eliminates the increased oxidative stress observed in these mice models. Hence, vitamin E is considered as a powerful antioxidant with anti-aging effect.

The National Institute on Aging Interventions Testing Program (ITP) examined the effects of compounds which are suggested to increase lifespan and prevent age-related disease in genetically heterogeneous mice. Significantly extended lifespan under nordihydroguaiaretic acid (NDGA) and aspirin supplementation for male mice was revealed by Strong et al. (2008). Aspirin, as a non-steroidal anti-inflammatory drug demonstrates anti-thrombotic and anti-oxidant properties (Shi et al. 1999; Vane 2000; Weissmann 1991). Aspirin activates the NF-kB signaling

pathway and induces apoptosis in two in vivo models of human colorectal cancer (Stark et al. 2007). NDGA has anti-oxidant and anti-inflammatory properties, moreover it demonstrates life-extension properties in metazoans (Wood et al. 2004). NDGA has been shown to prevent neuronal death and cognitive deficits which occurred under forebrain ischemia/reperfusion injury (Shishido et al. 2001). NDGA has an anti-cancer activity by affecting 5-lipoxygenase (Nony et al. 2005).

Anti-diabetic biguanides are considered as the most promising among pharmacological treatments of aging. This class of anti-aging compounds inhibits fatty acid oxidation, gluconeogenesis in the liver, increases the availability of insulin receptors and reduces excretion of glucocorticoid metabolites (Dilman 1994; Muntoni 1999). Metformin causes physiological and anti-aging effects similar to caloric restriction. Chronic metformin treatment enhanced mean and maximum lifespan of SHR mice, decreased body weight and slowed down the age-related switch-off of estrous function (Anisimov et al. 2008). However, metformin is not able to prevent tumor formation (Anisimov et al. 2008) and is toxic at high doses (Martin-Montalvo et al. 2013). The molecular mechanism of metformin action is by increasing activation of adenosine monophosphate-activated protein kinase (AMPK), which is involved in maintaining energy balance (Martin-Montalvo et al. 2013).

Positive effects of HDAC inhibitors on life- and health-span have been reproduced in numerous model organisms, including rodents. For instance, mice fed a high fat diet and additionally treated with SB (sodium butyrate), showed reduced obesity and insulin resistance (Gao et al. 2009). Also, SB induced insulin sensitivity and reduced adiposity in obese mice. The lifespan extension effect in mice by SB treatment is accompanied with functional improvement of myocardial function and also attenuation of cardiac hypertrophy and increased angiogenesis in myocardium (Chen et al. 2015). It is noteworthy that the level of superoxide dismutase was significantly enhanced in SB-treated diabetic mice (Chen et al. 2015). SB was also shown to be effective in treatment of neurodegenerative diseases which are associated with the aging process. Mice with neurodegenerative disease phenotype treated with SB demonstrated ameliorated defects in histone acetylation, thereby substantially improving motor performance and extended mean lifespan. A positive effect was observed under TSA administration, which resulted in increased mean survival time following the treatment (Yoo and Ko 2011).

Resveratrol is widely known for its properties to extend the lifespan of yeast, worms, and flies (Bhullar and Hubbard 2015). It is the best studied anti-aging drug, without known toxicity, with the ability to treat and counteract a number of age-related diseases such as cancer, Alzheimer's disease, and diabetes (Baur and Sinclair 2006; Hubbard and Sinclair 2014). It is interesting to note that resveratrol does not extend the lifespan of healthy mice (Pearson et al. 2008; Strong et al. 2013). However, resveratrol's lifespan extending effects were shown for metabolically compromised mice fed a high-calorie diet (Baur et al. 2006). It improved mitochondrial number, locomotor activity and increased insulin sensitivity. Resveratrol supplementation might be beneficial against environmental toxins, pathogens and radiation. Indeed, resveratrol restored renal microcirculation and extend lifespan in mice with kidney injury (Holthoff et al. 2011). Additionally, a protecting effect of

resveratrol on the tubular epithelium by scavenge reactive nitrogen species has been shown (Holthoff et al. 2012). It also improves longevity and prevents tumor formation in mice subjected to ionizing radiation (Oberdoerffer et al. 2008). A DR-mimicing effect of resveratrol treatment in lower organisms has been shown. Furthermore, resveratrol induces gene expression patterns that parallel those induced by DR (Pearson et al. 2008). Resveratrol-treated animals are characterized by a generalized reduction in oxidative stress and inflammation, which are consistent features of the DR effect. Besides improving insulin sensitivity and increasing survival in mice, resveratrol improves cardiovascular function, bone density, and motor coordination (Pearson et al. 2008).

TOR signaling inhibition was shown to extend lifespan in invertebrate models. A lifespan extension effect was demonstrated in mice of both sexes, which were treated late in life (aged 20 months) (Harrison et al. 2009; Miller et al. 2011). Furthermore, late rapamycin treatment reverses the age-related heart dysfunction and also resulted in beneficial skeletal, motor and behavioral changes (Flynn et al. 2013).

A significant body of evidence suggests an anti-aging effect for *Ludwigia octovalvis* (LOE) in mice. Indeed, it was demonstrated that this natural compound attenuated age-related cognitive decline in senescence-accelerated-prone 8 (SAMP8) mice (Lin et al. 2014). Hence, LOE can be proposed as a potential anti-aging compound for attenuating oxidative damage and activating AMPK-related pathways (Lin et al. 2014).

The Rat *Rattus norvegicus*

In addition to mice, rats are used extensively in studies related to aging. Early studies demonstrated a prolongevity effect following Vitamin E supplementation in male rats, which were reared on a high fat diet (Porta et al. 1980). This phenotype was associated with reduction of incidence of malignant neoplasms, but there was no influence on the incidence or severity of chronic nephropathy, which was developed in all rats (Porta et al. 1980).

Metformin, as a CR mimetic, was shown to extend lifespan in Fischer-344 rats, mostly by prevention of tumor formation (Smith et al. 2010). Furthermore, it significantly reduced body weight and adipose tissue (Muzumdar et al. 2008). However, CR has a stronger impact on median and maximum lifespan as compared to metformin treatment (Smith et al. 2010). It worth noting, however, that an effective dose for Fisher-344 rats was about tenfold higher than the maximum daily dose used in human treatment (Ma et al. 2007).

Low resveratrol (LR) doses and red wine (RW) supplementation both improved vascular function and aerobic capacity, moreover, they decrease markers of senescence (P53, P16) in rats. However, these experimental rats did not live longer (da Luz et al. 2012). The potential molecular mechanism of RW and LR action involve

ubiquitous NAD^+-dependent protein deacetylases. Resveratrol protects against oxidative stress via the Nrf2 pathway and, in turn, attenuates mortality in obese rats. Both acute and chronic resveratrol treatment improves post-ischemic cerebral perfusion in rats (Ritz et al. 2008a, b). Additionally, down-regulation of inducible NO synthase (iNOS) and up-regulation of vasorelaxant eNOS were observed in treated rats.

Rapamycin, as a potent and specific mTOR inhibitor, is widely used for treatment of renal cell carcinoma and mantle cell lymphoma, moreover, it is often tested in clinical trials as a therapeutic compound to cure various cancer types (Konings et al. 2009; Dancey 2010). Systemic chronic administration by rapamycin causes impaired glucose homeostasis in type 2 diabetes (Deblon et al. 2012). Furthermore, rapamycin prevents excessive body weight gain, fat accumulation and hepatic steatosis, however, it also leads to insulin resistance and glucose intolerance in rats fed a high-fat diet (Deblon et al. 2012). The molecular mechanism, underlying these effects is realized through insulin-related signaling pathways. Interestingly, rapamycin prevents spontaneous retinopathy in senescence-accelerated OXYS rats (Kolosova et al. 2012). Hence, rapamycin can be suggested as having therapeutic potential for treatment and prevention of age-associated pathologies.

The longevity phenotype under NDGA supplementation in flies (Miquel et al. 1982) and mice (Strong et al. 2008) was previously reported. Furthermore, there is evidence concerning the anti-aging effect of NDGA in rats (Buu-Hoi and Ratsimamang 1959). Interestingly, this longevity phenotype has been associated with enhanced glucose clearance, reduced triglycerides and insulin sensitivity in a diabetic rat model (Reed et al. 1999). The molecular mechanism of NDGA action are related to its ability to block fatty acid synthesis in adipocytes, through inhibition of fatty acid synthase and lipoprotein lipase (Li et al. 2005; Park and Pariza 2001).

Numerous studies have demonstrated the highly conserved effect of aspirin on lifespan and healthspan in different models. There was no direct impact of aspirin supplementation on rat survival. However, aspirin normalized blood pressure in rats with hypertension phenotype (Tuttle et al. 1988).

Conclusions from Animal Models

Testing chemical compounds for their ability to slow down aging in multiple species may support their usefulness in treating and retarding age-related disease in humans. Indeed, the main rationale for testing these compounds in animal models is to introduce them into clinical research and, in turn, improvement of human health and longevity. Model organisms, including *C. elegans, D. melanogaster* and rodents are important for understanding signaling pathways and genes related to aging, and the possibility to alter them with drugs or supplements. Here we have reviewed the publications showing that many compounds have a highly conserved effect on healthspan and lifespan across model organisms. Furthermore, the molecular

mechanism of their action and longevity pathways involved in ageing control are also often conserved. The reasonable question is now to ask is how we can extrapolate these data to humans? First of all, ageing is characterized by the occurrence of age-related diseases. For this reason, potential anti-aging compounds, which have a positive effect in preventing or treating some age-related disorders in animal models, should be thoroughly investigated in clinical trials. Secondly, it is important to emphasise possible side effect and any hormetic action of many pharmaceutical compounds. The optimal concentration differs in every animal model, and also should be individually assessed in each patient.

Most of the age-related diseases are characterized by accumulation of oxidative damage to macromolecules. Antioxidants such as N-acetylcysteine (NAC) and vitamin E prevent oxidative stress and in this way modulate longevity. Interestingly, the natural compound cocoa imparts its antioxidant properties to extend organismal lifespan. The formation of molecular aggregates is the major feature of numerous age-associated diseases including Parkinson's, Alzheimer's and Huntington's disease. Hence, formation of protein aggregates is an important indicator of aging. Both lithium and curcumin prevent protein aggregation and produce prolongevity phenotypes. Using *C. elegans* and *D. melanogaster* as model systems it was demonstrated that the pharmacological approach to maintain protein homeostasis might be promising to prevent pathology caused by age-related disease and extend lifespan. The best studied and robust means of extending the lifespan of model organisms is dietary intervention termed dietary restriction (DR). TOR and insulin signaling pathways have been shown to be important for modulating lifespan in animal models.

Hence, preclinical studies on *in vitro* models have established a large number of promising pharmaceutical compounds with proven anti-aging properties. Moreover, the possible direct or indirect molecular targets and mechanisms of action mediating these chemicals have been established. Chemical screens in animal models are particularly promising for the development of possible drugs for humans.

Beneficial Health Effects in Humans

Metformin

Metformin is inexpensive, safe and widely prescribed glucose-lowering drug, being the first-line treatment for patients with T2D, it was proven to effectively reduce risk of cardiovascular diseases and death (Chamberlain et al. 2017; Palmer et al. 2016). In older patients, use of metformin is accompanied by reduced risk of hypoglycaemia and non-fatal cardiovascular events, compared to other antidiabetic drugs (Schlender et al. 2017). Apart from its direct hypoglycemic effects and prevention of target-organ damage in T2D patients it has shown numerous advantageous effects in patients with diverse conditions such as impaired glucose tolerance (Hostalek

et al. 2015), obesity (Bouza et al. 2012; Siskind et al. 2016), metabolic syndrome (Zimbron et al. 2016), polycystic ovary syndrome (PCOS) (Patel and Shah 2017) and nonalcoholic fatty liver disease (Li et al. 2013).

Metabolic Effects of Metformin

Numerous pleiotropic metabolic effects of the hypoglycemic drug metformin have emerged during its clinical use. Metformin exerts its glucose-lowering effect via AMPK, which is also involved in the lipid metabolism regulation. AMPK phosphorylates and in this way inactivates acetyl-Co-A carboxylase, which plays essential role in the synthesis of fatty acids. One thousand and five hundred milligram per day metformin monotherapy has been shown to reduce total cholesterol, triglycerides, LDL-C and VLDL-C, increasing HDL-C levels (Garimella et al. 2016). A small study aimed to evaluate the effects of metformin on lipid peroxidation in T2D patients assigned to metformin, gliclazide or diet, showed a significant increase in activity of antioxidant enzymes in erythrocytes, along with malondialdehyde reduction in the metformin group compared to diet alone. These results suggested that administration of metformin might decrease oxidative stress in T2D subjects (Memisogullari et al. 2008).

Direct influence of metformin on insulin resistance, combined with leptin reduction and GLP-1-mediated lipolytic and anorectic effects contribute to weight loss in T2D patients and non-diabetic individuals (Rojas and Gomes 2013). Six months of metformin treatment in overweight and obese, mostly insulin-resistant patients resulted in significant weight loss in insulin-resistant group, comparing to untreated controls (Seifarth et al. 2013).

A systemic review and meta-analysis by Björkhem-Bergman and colleagues revealed that metformin, compared to placebo, caused a significant weight reduction in adults and children, treated with atypical antipsychotic medication (Björkhem-Bergman et al. 2011). Metformin was also shown to reduce amounts of advanced glycation end-products (AGEs) in patients with T2D and PCOS (Diamanti-Kandarakis et al. 2007; Haddad et al. 2016). AGEs contribute to cellular senescence and are linked to target-organ damage in T2D, neurodegeneration, inflammation and oncogenesis (Ott et al. 2014; Yamagishi et al. 2012). Metformin seems to reduce formation of AGEs through its hypoglycemic action and additionally by down-regulating expression of cellular receptors to AGEs, thus preventing activation of downstream signaling targets (Ishibashi et al. 2012).

Cardiovascular Effects of Metformin

Metformin is the only anti-diabetic drug, shown to reduce microvascular outcome, most likely due to its miscellaneous effects beyond glycemic control (Rojas and Gomes 2013). Sub-analysis of obese patients from one of the largest trials, the United Kingdom Prospective Diabetes study (UKPDS), intensively treated with

metformin, experienced a 33% reduction of myocardial infarction risk, compared to conventionally treated patients (American Diabetes Association 2002). During the 10 years follow-up a sustainable reduction in microvascular risk and reduction of risk of myocardial infarction and death from any cause was observed among overweight patients. These effects were thought to be exerted due to pleiotropic effects of metformin, not just due to glycemic action alone (Holman et al. 2008).

Papanas and coauthors concluded that metformin might also be beneficial for patients with heart failure, improving the 2-year survival. These authors have suggested that potential prevention of cardiac fibrosis could be mediated by AMPK-dependent mechanisms (Papanas et al. 2012). Experimental data also shows that metformin ameliorates endothelial function, phosphorylating eNOS and stimulating release of NO (Eriksson and Nyström 2015).

However, according to the recent meta-analysis performed by S.J. Griffin and colleagues, summarizing the reports from 13 trials (with 2079 individuals with type 2 diabetes allocated to metformin and a similar number to comparison groups), there is no certainty as to whether metformin reduces the risk of cardiovascular disease. In this review metformin reduced risk of all-cause mortality by up to 16% and at the same time, increased risk of stroke by up to 48%. The authors underlined the fact that cardiovascular endpoint data from studies of metformin is derived from a small studies with quite specified categories of patients – relatively young, overweight or obese, North American and Northern European – with poorly controlled diabetes, lacking evidence from older adults with HbA1c less than 8%, people of diverse ethnic group and geographical origin (Griffin et al. 2017).

Effects of Metformin on Inflammation

Chronic low-grade inflammation is an important pathogenetic mechanism involved in aging (Franceschi and Campisi 2014). Targeting inflammatory mechanisms has a promising contribution to human longevity and prevention of age-associated diseases (Fougère et al. 2017). Experimental data obtained from human cells shows that metformin inhibits IL-1β-induced release of the pro-inflammatory cytokines IL-6 and IL-8 in human vascular smooth muscle cells (SMCs), macrophages, and endothelial cells (ECs) in a dose-dependent manner. This study also demonstrated reduction in activation and nuclear translocation of nuclear factor-κB (NF-κB) in SMCs under metformin treatment, as well as suppression of pro-inflammatory phosphokinases Akt, p38, and Erk activation (Isoda et al. 2006).

Several studies have demonstrated anti-inflammatory pleiotropic effect of metformin in diabetic patients. A study by Chen et al. (2016) showed that compared to other antidiabetic drugs (gliclazide, acarbose, or repaglinide), metformin significantly reduced levels of proinflammatory cytokines (IL-6, TNF-α) in serum and MCP-1 in urine of T2D patients. These effects were time- and dose-dependent. The authors concluded that metformin reduces inflammatory responses in the systemic circulation and urine, thereby contributing to its beneficial effects on type 2 diabetes.

In a population cohort study, involving 3575 naïve T2D patients, Cameron and coauthors showed that compared to sulfonylurea treatment, metformin reduced the mean neutrophil to lymphocyte ratio, an inflammation marker and predictor of all-cause mortality and cardiac events (Cameron et al. 2016).

Anticarcinogenous Properties

There is an established increased risk of certain types of cancer in T2D patients. Numerous studies and meta-analyses showed an association between T2D and an increased risk of liver, pancreas, endometrial, colorectal, breast, and bladder cancer (Giovannucci et al. 2010). This association might have a causal reason, explained by hyperglycemia, insulin resistance and hyperinsulinemia, however the high prevalence of confounding factors such as adiposity in T2D patients could also have a potential influence on cancer incidence in this specific category of patients (Tsilidis et al. 2015).

Meta-analysis of studies, comparing metformin with other drugs in diabetic patients, demonstrated a 30% lower cancer incidence of all cancer types in metformin-allocated patients (Decensi et al. 2010). A recent systematic review assessed cancer risk and cancer mortality in 12 randomized controlled trials (21,595 patients) and 41 observational studies (1,029,389 patients). Metformin intake was associated with reduction of the cancer mortality risk, as well as risk of any cancer for 35% and 31%, respectively (Franciosi et al. 2013). Also, Zhang and coauthors demonstrated the preventive effect of metformin towards liver cancer. In T2D patients use of metformin was associated with 62% reduction in the estimated risk of liver cancer and 70% risk reduction for hepatocellular carcinoma (Zhang et al. 2012).

Li et al. (2017) analysed nine retrospective cohort studies and two RCTs for potential effects of metformin on survival of pancreatic cancer patients. Results showed significant improvement in survival of patients receiving metformin compared to controls. However, effects of metformin were insignificant in patients with advanced disease stages. Observational studies showed a reduced incidence of endometrial cancer (EC) in metformin-treated diabetic patients and improved the overall survival of patients with EC (Tang et al. 2017). Meireles et al. (2017) performed a systematic review and meta-analysis of studies assessing potential metformin effects in patients with endometrial hyperplasia and EC. Use of metformin was associated with reversion of atypical endometrial hyperplasia to a normal endometrium. There was also a significant decrease in expression of cell proliferation biomarkers. Metformin-treated EC patients had a higher overall survival compared to non-metformin users and non-diabetic patients. The authors suggested that EC patients might benefit from addition of metformin to standard treatment, considering the evidence of reversing atypical hyperplasia, cell proliferation biomarkers reduction and overall survival improvement.

A recent analysis by Hou and colleagues, including seven studies with 7178 participants, evaluated the impact of metformin treatment on the occurrence of colorectal adenoma (CRA) in T2D patients. Metformin therapy correlated with a significant decrease in the risk of CRA in the T2D patients, with a 27% reduction in comparison to T2D treatment without metformin (Hou et al. 2017). Other meta-analysis showed improved overall survival in colorectal cancer patients, however no improvement in cancer survival (Meng et al. 2017).

The protective effect of metformin against breast cancer (BC) was summarized by Col et al. (2012) in postmenopausal diabetic women. Meta-analysis of 11 studies, including 5464 BC patients with diabetes (2760 patients who had received metformin and 2704 patients who had not) showed that metformin use was associated with a 47% decreased risk of death from all causes in BC patients with diabetes, as well as with reduced cancer-related mortality. After adjusting patients for hormonal receptor expression, metformin showed improvement in overall survival by 65% (Xu et al. 2015). Recently, metformin demonstrated its potential role as an additional cancer-treatment option in non-diabetic BC patients, by unveiling indirect insulin-dependent effects of intervention. Women with newly diagnosed, treatment-naïve, early-stage BC were recruited for participation in the study, regardless of tumor subtype. Patients were administered 500 mg of metformin three times daily for about 2 weeks after diagnostic core biopsy until the moment of surgery. Tumor biopsies were collected prior to metformin administration and after the surgery. Immunohistochemical analysis of tumors demonstrated the reduction in PKB/Akt and ERK1/2 phosphorylation, decreased insulin receptor expression in the tumor, reduction in PI3K and Ras-MAPK signaling following metformin administration. Researchers claim that fasting insulin levels and insulin receptor expression by the tumor cells could possibly stratify patients to further allocate them for metformin treatment (Dowling et al. 2015). Analysis by Yu et al. suggests that metformin use appears to be associated with a significant reduction in the cancer risk and biochemical recurrence of prostate cancer (Yu et al. 2014).

A retrospective cohort study by Tseng C-H., pointed out that metformin significantly reduces gastric cancer risk, especially when the cumulative treatment duration is more than ~2 years (Tseng 2016). Meta-analysis of cohort studies revealed that the risk of gastric cancer among patients with T2D is lower in metformin-users, compared to those who were not treated with metformin (Zhou et al. 2017).

However, data from different meta-analysis on cancer incidence and mortality among metformin users is often conflicting due to diverse analysis methodology, heterogeneity of studies, absence of cancer data in some studies and short follow up time (Stevens et al. 2012). Due to potential causal interpretation of findings and observational nature of studies, often included into meta-analysis, this is identified as another limitation (Col et al. 2012). Even when considering the epidemiologically proven anticarcinogenous effects of metformin, the exact mechanisms of tumor suppression remain essentially unknown. Researchers suggest the potential direct effect on cancer cells to be via AMPK-mediated mechanisms and mammalian target of rapamycin (mTOR) inhibition (Col et al. 2012). Other possible mechanisms include

inhibition of the HER2 and NF-κB signaling pathways (Lei et al. 2017). There is an ongoing discussion and research as to whether metformin should be introduced into cancer treatment as a strategy to improve survival, however the question whether non-diabetic cancer patients will surely benefit from this treatment remains open.

Prevention of Frailty in Elderly Patients

Frailty is a complex geriatric syndrome, associated with increased risk of death in elderly patients, and could be potentially prevented or influenced by metformin. Comparison of metformin-treated patients vs. metformin-naïve showed reduction of frailty risk and comorbidity in elderly T2D patients (Sumantri et al. 2014). Metformin-treated patients, included in this study also demonstrated better muscle strength and body balance characteristics. Previously, a study by Musi et al. (2002) described enhanced AMPK phosphorylation and glucose uptake in muscle tissue of metformin-treated diabetes subjects, which might partially explain better frailty indexes under metformin treatment. Another study by Gore and colleagues demonstrated enhanced muscle protein anabolism of metformin in intensive care patients with severe burns. Patients treated with metformin groups experienced increased fractional synthetic rate of muscle protein and the greater net rate of phenylalanine deposition into the leg, compared to placebo (Gore et al. 2005). The cohort study by Wang et al. (2014) suggested that metformin could be associated with reduced mortality mediated by reducing the onset of frailty older adults with T2DM. Compared to the sulfonylureas, metformin treatment was significantly associated with decreased incidence of frailty in the studied cohort. Some success was demonstrated metformin-associated prevention of osteoporosis in experimental models (Gao et al. 2010; Mai et al. 2011; Tolosa et al. 2013). However, a 12-week study by S.K. Hegasy failed to show improvement of bone-turnover markers in metformin-treated postmenopausal diabetic women, compared to the study baseline (Hegazy 2015). Perhaps, studies with larger numbers of subjects and longer-follow-up are required to clearly establish effects of metformin on osteogenesis and bone tissue loss in susceptible elderly populations.

Metformin and Cognitive Function

Currently there is conflicting evidence about the effects of metformin on cognitive decline in elderly individuals. Certain studies, involving diabetic patients, emphasized the protective role of metformin against cognitive decline, others, on contrary claimed that exposure to metformin contributes to neurodegeneration, Parkinson and Alzheimer disease. Contradicting results of these studies are explained by prevalent comorbidity of T2D patients, necessity to prescribe more than one medication and practical impossibility to evaluate the exclusive effect of metformin alone. Cognitive decline could also potentially arise from other concomitant conditions,

not necessarily stemming from pharmacological intervention of any sort. Cross-sectional study by D. Hervás and colleagues showed that the use of metformin was associated with better cognitive function in patients with Huntington's disease (Hervás et al. 2017).

Longitudinal multivariate analysis in the population-based Singapore Longitudinal Aging Study showed a significant inverse association of metformin use and cognitive impairment in T2D patients, controlling for age, education, diabetes duration, fasting blood glucose, vascular and non-vascular risk factors. This study also showed a linear trend of the lowest risk for cognitive decline under use of metformin for longer than 6 years, in cross-sectional and longitudinal analysis. The authors of this study concluded that long-term metformin treatment in T2D patients might reduce the risk of dementia and cognitive impairment (Ng et al. 2014).

In a cohort study of Taiwan's National Health Insurance Research Database, 4651 patients were recruited in the metformin cohort and a comparable number of non-metformin controls, by using propensity score matching. During the 12 year follow-up it was demonstrated that metformin users had a higher risk of Parkinson's disease, along with an increased risk of all-cause dementia, risk of Alzheimer's disease, and vascular dementia. Time and dose-dependent effects were observed for occurrence of Parkinson's disease and dementia (Kuan et al. 2017).

Undoubtedly, there is a strong need for further large-scale prospective controlled trials, focusing on cognitive function of patients allocated to metformin. Recently, several promising studies, evaluating the exclusive role of metformin, as an anti-aging agent with emphasis on age-related diseases in humans have been designed and launched. The Metformin in Longevity Study (MILES) aims to determine whether 1700 mg/daily metformin can potentially restore gene expression in elderly with impaired glucose tolerance (https://clinicaltrials.gov/ct2/show/NCT02432287?term=metformin&cond=Ageing&rank=2). The Targeting Aging with Metformin (TAME) trial is designed as a first randomized controlled clinical study to evaluate metformin as an anti-aging drug. Primary trial outcome is the time until occurrence of any of aging-related multimorbidity composite (coronary heart disease, stroke, congestive heart failure, peripheral arterial disease, cancer, T2D, cognitive impairment, mortality) (Newman et al. 2016) (https://www.afar.org/natgeo/).

Rapamycin and Rapalogs

Rapamycin (sirolimus) is an mTOR inhibitor, widely used for immunosuppression for organ transplant recipients and cancer patients (Blagosklonny 2017). Some of the common adverse reactions observed upon administration of rapamycin in clinical trials include hypertriglyceridaemia, hypertension, hypercholesterolaemia, creatinine increase, urinary tract infection, anaemia and thrombocytopaenia. Currently, several rapalogs with pharmacokinetic properties superior to rapamycin and reduced immunosuppressive effects are being tested as immunosuppressant or treatment options for advanced solid tumors (Xie et al. 2016).

After numerous animal studies, rapamycin is widely discussed as a medicamentous intervention to increase healthspan and longevity in humans. Potential highlights of its use in prevention of certain age-related diseases and conditions should be obtained from follow-up studies, performed on cohorts, where rapamycin is used according to its primary indication – as immunosuppressant or cytostatic drug.

Evidence from clinical trials suggests that continuous use of mTOR inhibitors in transplant patients increases risk of diabetes. Data from the United States Renal Data System, evaluating association of sirolimus use in 20,124 adult kidney recipients without diabetes, concludes that patients on sirolimus are at increased risk of new-onset diabetes, compared to subjects on other immunosuppression schemes. This risk did not depend on the immunosuppressant combination, in which mTOR inhibitor was initially prescribed to the patient (Johnston et al. 2008). However, the exclusive role of rapamycin in onset of diabetes is very difficult to evaluate. On the contrary, patients after kidney transplantation, converted to rapalog everolimus, experienced reduced risks of diabetes mellitus in meta-analysis of RCTs (Liu et al. 2017a, b). Risk of diabetes in post-transplant patients is also negotiable due to potential investment of other medications into pathophysiology of abnormal glucose metabolism and initial risk factors of the given population. It remains unclear whether chronic use of rapamycin might result in hyperglycemia and diabetes in healthy individuals, thus future studies are warranted (Blagosklonny 2012a, b). Another known side effect of rapalogs, occurring in 40–75% of patients is dyslipidemia (Kurdi et al. 2018). Rapamycin altered levels of serum lipids in patients with autosomal-dominant polycystic kidney disease (ADPKD), increasing serum total cholesterol, triglycerides and LDL-C, however without influencing HDL-C (Liu et al. 2014a, b). Several authors suggest that combined use of mTOR inhibitor with medications capable of controling adverse effects of rapalogs, such as statins and metformin might be a promising combined formula to control age-associated diseases (Martinet et al. 2014; Blagosklonny 2017).

Despite certain pro-atherogenic effects, local application of sirolimus is widely used for revascularization interventions in patients with coronary artery diseases. Sirolimus-eluting stents (SES) demonstrated to reduce the short-, long- and overall-term risk of target lesion revascularization (TLR) and target vessel revascularization, as restenosis, major adverse cardiac events (MACE), overall-term risk of myocardial infarction in randomized controlled trials, comparing SES with paclitaxel-eluted scaffolds (Zhang et al. 2014). Another study, including population of 2877 patients, who underwent stenting with polymer-free sirolimus-coated scaffolds, demonstrated favorable rates of TLR and MACE reduction (Krackhardt et al. 2017).

mTOR inhibitors can cause regression of atherosclerosis with subsequent artery lumen enlargement and plaque regression. Thr underlying mechanisms of these interventions are not precisely understood; Martinet and coauthors hypothesize that these outcomes arise from cell proliferation suppression, modulation of authophagy, cell survival and cholesterol efflux. Currently, there is no evidence that systemic administration of mTOR inhibitor might be beneficial in dyslipidemia and atherosclerosis prevention. On the contrary, systemic mTOR inhibitor use is associ-

ated with dyslipidemia and hyperglycemia, risk factors, contributing to plaque formation and destabilization (Martinet et al. 2014).

Inhibitors of mTOR showed certain positive effects in transplant recipients in several collaborative studies and meta-analyses. Based on data from 6867 patients in 21 randomized trials, it was found that sirolimus use was associated with a 40% reduction of malignancy risk after kidney or combined pancreatic and kidney transplantation. This meta-analysis also showed 56% reduction of non-melanoma skin cancer (NMSC) risk, compared to non-sirolimus immunosuppression. These authors concluded that a cancer-protective effect was even more obvious in those patients who converted to sirolimus treatment after an established regimen of immunosuppression; this intervention resulted in reduction of NMSC risk and other cancers. However, sirolimus administration, both de novo and after switch from other immunosuppression agent, was associated with an increased risk of death, compared to controls (Knoll et al. 2014).

The Collaborative Transplant Study involved 78,146 patients after kidney transplantation, receiving either mTOR inhibitor, or non-mTOR-inhibitor immunosuppressant demonstrated that kidney transplant recipients, receiving mTOR inhibitor de novo have had reduced incidence of NMSC, however no influence on other cancers was found (Opelz et al. 2016).

Many oncogenic pathways, including the Ras/Raf/MEK/ERK pathway and the phosphoinositide 3-kinase (PI3K)/AKT (PKB) pathway are linked to mTOR signalling. Approximately 70% of human tumors harbor gain-of-function mutations in oncogenes (i.e. PI3K, AKT, or Ras) and/or loss-of-function mutations in tumor suppressors (i.e. PTEN, LKB1 or TSC1/2), resulting in mTORC1 hyperactivation (Forbes et al. 2011; Li et al. 2014). Inhibition of mTOR appears to be a promising approach in oncology, as this molecular target is involved in cell proliferation, metabolism, angiogenesis, survival, and is involved in cancer development and immune microenvironment modulation (Cash et al. 2015). mTOR inhibitors (everolimus, serolimus or temsirolimus) were also shown to improve the effects of hormonal therapy and the outcome in patients with metastatic luminal breast cancer. It was suggested that mTOR inhibition might affect hormone sensitivity of the tumor cells (Rotundo et al. 2016).

A recent Cochrane review and meta-analysis revealed beneficial effects of rapamycin and rapalogs on tuberous sclerosis – rare multisystem disease with formation of benign tumors and neurological disorders. Results of 3 placebo-controlled studies with a total of 263 participants demonstrated, that administration of everolimus achieved a 50% reduction in the size of sub-ependymal giant cell astrocytoma and renal angiomyolipoma. Sasongko and coauthors concluded that use of rapalogs in clinical practice is supported by significant evidence, as the benefits outweigh the risks, as risk of adverse events among treated patients was the same as in those who received no treatment (Sasongko et al. 2016).

One of the main concerns regarding chronic use of rapalogs is related to suppression of the immune system and potential high susceptibility to infection, including opportunistic infections, fatal infections, sepsis (https://www.rxlist.com/rapamune-drug.htm). Meta-analysis of RCTs, evaluating sirolimus for treatment of ADPKD

showed a slight increase of the rate of infection (generally aphtous stomatitis and pharyngitis), yet its use was not associated with induction of severe infections (Liu et al. 2014a, b). Recent meta-analysis revealed that treatment with mTOR inhibitors in patients with lymphangioleiomyomatosis, a chronic destructive cystic lung disease, does not appear to increase the incidence of respiratory infections. On the contrary, sirolimus and everolimus demonstrated a trend towards reduction of respiratory infection risk, compared to placebo. The authors underline the point that additional studies are warranted to determine the mechanism of the potential protective effect of mTOR inhibitors, which may involve numerous mechanisms in the respiratory tract, immune system and microbiome (Courtwright et al. 2017).

It is also necessary to underline the fact that rapamycin is used for immunosuppression only in specific categories of transplant recipients. I.e., the FDA issued a black box warning towards use of sirolimus in liver transplant patients. De novo use of sirolimus in post-liver transplant patients was associated with high incidence of hepatic artery thrombosis and decreased patient and graft survival. Massoud and Wiesner (2012) reported a controversial role of rapamycin in liver transplant recipients, showing potential benefit of its use in liver transplant patients with hepatocellular carcinoma (HCC) (sirulimus appears to increase recurrence-free survival for liver recipients due to HCC) (Chinnakotla et al. 2009). They underlined the need for further evaluation of anti-neoplastic and anti-viral effects of sirolimus, potentially favorable for certain categories of liver recipients (Massoud and Wiesner 2012). Sirolimus previously demonstrated suppression of hepatitis C recurrence in a small cohort of liver transplantation candidates (Wagner et al. 2010). A later study by Yanik and colleagues showed that HCC recurrence and cancer-specific mortality rates were lower in patients prescribed with sirolimus, but not statistically significant. This study also demonstrated more favorable outcomes in patients older than 55 years, while younger patients had worse outcomes, including all-cause mortality, HCC recurrence and cancer-specific mortality (Yanik et al. 2016).

Evaluating the effects of rapamycin on aging, its biomarkers and age-related diseases in humans appears to be a very challenging task. This drug is used in very specific patient populations – transplant recipients, who often experience multimorbidity, initial functional decline in many physiological parameters along with the strong need to take several medications to control immune response against the graft and provide proper nephroprotection (Lamming et al. 2013). Better prognosis and rate of certain outcomes in these subjects could be also explained by direct immunosuppressive effects of rapamycin, preventing graft rejection and preserving renal function, thus reducing the impact of renal- dependent mechanisms. It is necessary to highlight the fact that most of the data regarding pleiotropic actions of rapalogs come from small, retrospective, case-control studies. A pilot randomized control trial, establishing feasibility of rapamycin in a small group of overall healthy volunteers aged 70–95 years, showed that 1 mg of this agent can be safely used in short-term settings. The reported findings on cognitive, physical performance and immune changes are rather occasionally anecdotal than consistent, and do not enable one to draw a firm conclusions. Larger trials with longer treatment duration

are warranted for further analysis, interpretation and possible practical translation (Kraig et al. 2018).

An additional large concern in case of chronic rapamycin administration in women of reproductive age is its potential embryo- and fetotoxicity. No proper controlled studies have been conducted in pregnant women, thus the FDA marks this agent as pregnancy category C, recommending avoiding pregnancy and nursing during rapamycin therapy (https://www.rxlist.com/rapamune-drug.htm). Use of rapamycin in healthy individuals to control mechanisms involved into aging remains a widely discussible and negotiable intervention, considering the balance between potential risks and beneficial outcome. Nevertheless, toxicity issues might be successfully addressed by targeted drug delivery, allowing rapamycin to be introduced as a senolytic drug to specific cell types or tissues. These technologies are already being developed and tested in preclinical settings (Gholizadeh et al. 2017; Thapa et al. 2017).

Aspirin

Aspirin (acetylsalicylic acid, ASA) is one of the top-prescribed medications worldwide. This agent made a historical entry from being originally developed as analgesic and antipyretic drug; nowadays is predominantly used for primary and secondary cardiovascular prevention. Yet, many of its complementary effects regarding age-related diseases are still to be unveiled (Desborough and Keeling 2017). Aspirin might be one of the most appropriate agents to be appointed as a promising anti-aging drug due to low costs and simplicity of treatment and well-investigated multifaceted properties regarding cardiovascular disease (CVD) and cancer.

Aspirin and CVD

Low-dose aspirin is an anti-platelet therapy with established clinically benefit in secondary prevention of cardiovascular diseases. The anti-platelet effect of aspirin results from COX-1 acetylation with subsequent inhibited production of thromboxane A_2. Growing evidence suggests, that aspirin-mediated acetylation might play additional, non-COX-dependent role in thrombosis prevention, together with anti-inflammatory and anti-tumor effects of this drug (Ornelas et al. 2017; Warner et al. 2011).

Currently, ASA is recommended to patients presenting with ST-elevation myocardial infarction (STEMI) and non-STEMI patients. A convincing body of evidence suggests that aspirin provides a beneficial reduction of CVD mortality and new CVD events (Ittaman et al. 2014). In non-STEMI, ASA is recommended to be prescribed to all patients without contraindications, using an initial loading dose (150–300 mg), followed by maintenance dose 75–100 mg daily for a long term, regardless whether an invasive or non-invasive treatment strategy was selected

(Roffi et al. 2016). Aspirin administration is recommended indefinitely in all patients with STEMI (Ibanez et al. 2018).

Meanwhile, the role of low-dose aspirin in primary prevention remains unclear (Brotons et al. 2015). Recent meta-analysis of 9 trials, where aspirin was used for primary cardiovascular prevention and involved 100,076 patients, showed that long-term aspirin in comparison to placebo or no aspirin reduced myocardial infarction, ischemic stroke, and all-cause mortality. Yet, this intervention increased risk of hemorrhagic complications – hemorrhagic stroke, major bleeding, and gastrointestinal bleeding. Raju et al. (2016) concluded that this prevention strategy always requires an evaluation of the balance between the potential benefit and harm of long-term ASA prescription; the shown reduction of all-cause mortality is a favorable fact deserving to be taken into account. Yet a high risk of bleeding, especially intracerebral hemorrhage remains the major concern for different patient cohorts, despite potentially favorable cardiovascular outcome. The clinical decision about prescription of low-dosed ASA in primary prevention remains complicated and requires evaluation of risk-benefit ratio for each individual. Additionally, selection of correct dose, coated/non-coated form of the drug, considering concomitant conditions and medications, possible twice-a-day dosing in patients with increased platelet turnover are among variables to be considered and further researched (Leggio et al. 2017).

Anti-cancer Effects of Aspirin

A large body of evidence exists on certain roles of chronic ASA administration in cancer prevention and cancer survival. Massive-scale meta-analysis, involving 23 RCTs on low-dose aspirin and non-vascular deaths reported significant reduction of cancer deaths; a preventive effect was observed after 4 years of aspirin intake (Mills et al. 2012). Results of meta-analyses suggest that aspirin might serve as a preventive treatment for breast cancer (Lu et al. 2017; Luo et al. 2012; Zhong et al. 2015a, b), prostate (Huang et al. 2014; Liu et al. 2014a, b), pancreatic (Zhang et al. 2015) and gastric cancer (Huang et al. 2017; Kong et al. 2016). Protective effects were not prominent in some cancer types, however these findings could have different explanations. For instance, meta-analysis by Hochmuth et al. (2016) demonstrated protective effect of ASA against non-small cell lung cancer with strong heterogeneity. Researchers assume that aspirin potentially prevents lung cancer, but only in certain patient populations, while others do not benefit.

Chronic use of aspirin was shown to provide certain benefits for patients with established cancer diagnosis, improving overall survival, reducing risk of cardiovascular events and in some cases influencing cancer-related survival, and slowing the rate of metastasis. Meta-analyses of trials regarding aspirin use in patients with different types of cancer often provide conflicting results due to variability in research methodology and large heterogeneity of available studies. E.g., meta-analysis of observational studies by Zhong et al. (2015a, b) reported a small if any effect of aspirin intake on survival of breast cancer patients. Another meta-analysis, demon-

strated decreased rates of breast cancer specific mortality, all-cause mortality and metastasis in aspirin and non-steroidal anti-inflammatory drug (NSAID) users. Beneficial effects of breast cancer survival were observed only if treatment was initiated after diagnosis, not before (Huang et al. 2015).

Aspirin intake was inversely related with prostate-cancer-specific mortality, according to meta-analysis by Li et al. (2014). A systematic review and meta-analysis by P.C. Elwood et al. concluded that low-dose aspirin is beneficial agent for adjuvant treatment of cancer. It was shown to reduce mortality in colon cancer, specifically in tumors, expressing *PIK3CA*. Probable and possible benefits were also demonstrated for breast cancer and prostate cancer patients. The authors emphasise that there is large heterogeneity among analyzed studies, with a lack of adequately planned and controlled randomized trials for less common types of cancers. Apart from that, reduction of vascular events and suppression of metastatic growth is promising evidence, allowing clinicians to discuss and incorporate aspirin as additional anti-cancer treatment into patients' treatments (Elwood et al. 2016).

The most remarkable chemopreventive and disease-modifying effects of ASA were observed in case of colorectal cancer (CRC). Current evidence even inspired US preventive services task force to recommend low-dose aspirin for primary prevention of CVD and CRC in adults aged 50–59, having ≥10% 10-year risk of CVD and are not at increased risk of bleeding (Chubak et al. 2015; Patrignani and Patrono 2016).

Meta-analysis by Ye et al. (2013) showed that low-dose (75–325 mg daily) regular (two to seven times a week) aspirin treatment lasting more than 5 years provides effective CRC risk reduction. Evidence from studies investigating CVD primary and secondary prevention suggested that ASA administration reduces the incidence of CRC, and CRC-mortality 10 years after treatment initiation (Chubak et al. 2016). Aspirin intake provides survival benefits for CRC-patients. Findings from meta-analyses of studies, evaluating aspirin use in patients with CRC demonstrated benefit in overall survival only in cases when aspirin was administered after cancer diagnosis. Meta-analyses suggest that post-diagnosis use of aspirin might be beneficial in CRC patients with positive expression of *COX-2* and *PIK3CA* mutated tumors, reducing overall mortality in *PIK3CA* mutated cancers by 29% (Li et al. 2015; Paleari et al. 2016).

Emillson and colleagues examined whether ASA intake might be an effective alternative to available CRC screening methods. Network meta-analysis compared efficacy of low-dose aspirin vs. flexible sigmoidoscopy or guaiac-based fecal occult blood test in reduction of colorectal cancer incidence and mortality. Low-dose aspirin seemed to be as effective as screening tools in colorectal cancer prevention, with effects more visible for malignancies with proximal colon localization. Randomized controlled trials are warranted to make a definite conclusion about possible colorectal cancer chemoprevention with ASA (Emillson et al. 2017).

ASA could be used for CRC prevention in susceptible populations, e.g. hereditary cancers like Lynch syndrome. The randomized trial CAPP2 (Cancer Prevention Programme) involved 861 participants with Lynch syndrome. Patients received 600 mg aspirin or placebo for up to 4 years. Intake of aspirin resulted in substantial

(around 60%) decrease of cancer incidence (Burn et al. 2011). Results from 1858 participants of Colon Cancer Family Registry support evidence that aspirin is effective to reduce risk of CRC in *MMR* gene mutation carriers (Ait Ouakrim et al. 2015). Aspirin could be pa romising agent for secondary chemoprevention in CRC patients who already have experienced an intervention due to confirmed CRC diagnosis. Meta-analysis of 15 RCTs, evaluating 10 different candidate chemoprevention agents among individuals with previous colorectal neoplasia, showed that non-aspirin NSAIDs were the most effective agents for prevention of advanced metachronous neoplasia. Low-dose aspirin, being second in efficacy, also demonstrated the most favorable safety profile. According to the results of this analysis, low-dose aspirin with superior risk/benefit profile might be considered for secondary colorectal cancer chemoprevention in patients with previous colorectal neoplasia (Dulai et al. 2016).

Anti-neoplastic effects of ASA include mechanisms related to COX-1 and COX-2 inhibition, however an increasing body of evidence also supports the hypothesis about non-COX mechanisms. COX-2 inhibition is considered to be crucial in prevention of colorectal neoplasia (Chubak et al. 2015). Discussion about possible mechanisms and pathways involved into carcinogenesis inhibition include inhibition of IκB kinase β, preventing activation of NF-κB, inhibition of extracellular-signal-regulated kinase (ERK) and Wnt/ β-catenin pathway (Alfonso et al. 2014). Aspirin was also shown to activate AMPK, which further inhibits activity of mTORC1 (Din et al. 2012; Lamming et al. 2013).

It is necessary to emphasise that future studies, evaluating the role of aspirin as a chemopreventive and/or adjuvant cancer treatment are warranted. Many studies report beneficial effects of ASA only if intake was initiated after cancer diagnosis, dose and treatment duration might also matter and vary in each case. Cancer prevention in specific patient cohorts at high risk of neoplasia (e.g. genetic cancers) is an increasingly interesting direction for future research.

Anti-inflammatory Properties of Aspirin

Direct COX-inhibition mediated mechanisms and indirect modulation of NF-kB pathway, along with inhibition of IL-7 release control the anti-inflammatory properties of ASA (Ornelas et al. 2017). Limited, but promising evidence exists about the role of aspirin in prevention of sepsis – life-threatening condition, often affecting elderly. An individual patient data meta-analysis with propensity matching showed 7–12% mortality risk reduction in sepsis patients, taking aspirin prior to sepsis onset (Trauer et al. 2017). The aspirin to Inhibit SEPSIS (ANTISEPSIS) trial is substudy of ASPirin in Reducing Events in the Elderly (ASPREE) to be finished in 2018; it is expected to answer the questions as to whether low-dose aspirin reduces sepsis-related mortality and sepsis related hospital admissions in elderly (Eisen et al. 2017).

Aspirin and Cognitive Function

Antiplatelet effects could provide potential benefits in neuroprotection, reducing impairments occurring as a result of small neurovascular lesions. However, data regarding possible buffering of cognitive decline among aspirin users is not that optimistic. Specific influence of ASA on brain white matter lesions (WML) was evaluated in patients from Women's Health Initiative Memory Study of Magnetic Resonance Imaging study. There was no significant difference between WML volumes among aspirin users and non-users (Holcombe et al. 2017). Furthermore, research, conducted in patients with Alzheimer's disease concludes that ASA use does not provide any additional therapeutic benefit; furthermore, due to increased risk of intracerebral hemorrhage, this exposes patients to high risk of additional cognitive loss (Thoonsen et al. 2010). Recent meta-analysis by Veronese et al. (2017) involving data from 36,196 patients does not confirm protective effect of aspirin towards cognitive decline in older age. Pooled data from RCTs and observational studies showed that use of low-dose aspirin was not associated with significantly better global cognition, or onset of dementia or cognitive impairment. Results of an ongoing the ASPREE trial (ASPirin in Reducing Events in the Elderly), assessing role of aspirin in maintenance of disability-free and dementia-free life in a healthy population of elderly is expected to be finished by the end of 2018. Use of sophisticated neurovisualization techniques in this study could be advantageous for better understanding of prevention of microvascular dementia with ASA. Trial is also aimed to evaluate whether potential benefits outweigh the risks in this specific population (McNeil et al. 2017).

Statins

Statins represent a heterogeneous group of pharmacological agents, mediating their lipid-lowering effects by 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibition. Statins are the most commonly used prescription drugs for the treatment of dyslipidemia due to their well-established cholesterol-lowering properties and reduction of cardiovascular events and mortality (Collins et al. 2016). Apart from their primary mechanism of action, involving hepatic cholesterol synthesis inhibition, statins exert multiple pleiotropic effects, independently of LDL-C lowering mechanisms. Statins inhibit synthesis of certain substances – farnesyl pyrophosphate, geranylgeranyl pyrophosphate, isopentanyl adenosine, dolichols and polyisoprenoid side chains of ubiquinone, heme A and nuclear lamins, classified as isoprenoid intermediates and playing key role in activation of numerous intracellular signaling proteins. Reduction of circulating isoprenoid intermediates affects activity of Ras and Ras-like proteins (Rho, Rab, Rac, Ral, and Rap). Thus, statins have anti-inflammatory, immunomodulatory, antioxidant, antiproliferative effects,

stabilize atherosclerotic plaques and prevent aggregation of platelets; each of these effects are cholesterol-independent and mediated via isoprenoid-dependent signaling pathways (Kavalipati et al. 2015; Oesterle et al. 2017). These additional properties along with long-term use safety and cost-efficiency promote potential repurposing of statins for treatment and prevention of multiple age-related diseases and conditions.

Cardiovascular Effects of Statins

An impressive body of evidence from multiple high-quality randomized clinical trials confirms that statins effectively reduce total cholesterol, LDL-C, risk of acute coronary syndrome, stroke, venous thromboembolic disease, and death (Chou et al. 2016; Fulcher et al. 2015; Taylor et al. 2013).

Meta-analysis of 92 placebo-controlled and active-comparator trials demonstrated that statins are affective for both primary and secondary cardiovascular prevention as a class, significantly reducing major coronary events and all-cause mortality. Among atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin, consistently strong evidence of benefit was provided for use of atorvastatin and simvastatin (Naci et al. 2013).

There is a gap in guidelines related to primary cardiovascular prevention with statins in elderly patients, due to the fact that most of the data on primary prevention was derived from patients at age 40–75. Huge concerns are related to potential side-effects of these agents in older patients, however, and many health professional address this issue and emphasize that potential benefits often outweigh risk of undesired side-effects (Mortensen and Falk 2018; Otto 2016).

Additional Benefits in CVD Prevention in T2DM Patients

Atorvastatin was shown to reduce the amount of glyceraldehyde-derived advanced glycation end-products in patients with acute myocardial infarction, thus, being important evidence of potential cardiovascular protection via reduction of AGE-RAGE signalling and oxidative stress (Shimomura et al. 2016). Significant decrease in serum AGEs was observed after 3 and 6 months of simvastatin treatment in elderly with hyperlipidaemia (Yang et al. 2016). Another study confirms that statins mediate decrease of plasma AGEs, contributing to plaque stabilization and lack of its progression in patients with acute coronary syndrome. Fukushima et al. (2013) showed that pitavastatin, but not atorvastatin significantly reduced serum levels of AGEs.

Anti-inflammatory Effects

Statins demonstrate convincing clinical benefit by reduction of inflammatory markers, making the use of statin for the treatment of chronic inflammatory diseases very appealing (Gilbert et al. 2017). Possible mechanism of anti-inflammatory effects of statins could be related to Ras-prenylation inhibition, resulting in beneficial reduction of C-reactive protein (CRP), including hs-CRP. Some studies confirm hs-CRP as being a non-conventional cardiovascular risk factor and predictor for the clinical outcome (Joo 2012; Kitagawa et al. 2017; Ridker 2016). Meta-analysis of statin use after revascularization marked beneficial modulation of systemic inflammatory markers in a group of statin-treated patients, followed by reduction of risk for postoperative atrial fibrillation (An et al. 2017). Recent meta-analysis of RCTs, evaluating statin use among patients with rheumatoid arthritis showed additional benefits of atorvastatin for management of RA. Atorvastatin was shown to decrease the levels of inflammatory markers – C-reactive protein and erythrocyte sedimentation rate, along with decrease in DAS28 score. This meta-analysis demonstrated superior anti-inflammatory properties of atorvastatin, compared to simvastatin (Li et al. 2018). Chronic low-grade inflammation, thus supporting aging, might be targeted with this group of agents.

Potential Anti-infectious Properties

Conflicting evidence exists regarding potential effects of statins as agents that reduce the risk of infectious diseases. Some of them, being substances of fungal origin, are widely discussed to have beneficial antimicrobial effects, also claimed as potential agents to fight microbial antibiotic resistance. Simvastatin is even considered to be repurposed as a novel adjuvant antibiotic (Ko et al. 2017). Among patients with drug-treated T2DM statins were associated with a reduced risk of infections (Pouwels et al. 2016). However, large meta-analyses showed no effect of statins on the risk of infections or deaths, related to infections (Deshpande et al. 2015; van den Hoek et al. 2011).

There is also a wide discussion related to utilization of statins as antiviral agents, including treatment of dangerous infections, like influenza (Mehrbod et al. 2014) and HIV (Kelesidis, 2012). Meta-analysis of 16 homogeneous studies showed that statins as adjuvant therapy, improved sustained virological response rate by 31% in patients with chronic hepatitis C infection, compared with those who obtained antiviral treatment alone. HCV-infected patients, receiving statins also had reduced risks of HCC, cirrhosis and mortality (Zheng et al. 2017).

Anticarcinogenous Properties of Statins

Numerous meta-analyses have addressed the potential role of statins in chemoprevention of cancer. Thus, it was shown, that use of statins can reduce the risk of colorectal (8–12%), gastric (27–44%), hematological (19%), liver (37–42%), oesophageal (14–28%), ovarian (21%) and prostate cancer (7%) (Undela et al. 2017).

Apart from lipid-lowering actions, which could potentially contribute to repression of tumor growth, statins interfere with several pathways which modulate carcinogenesis. Statins demonstrate multi-level anti-cancer functions, modulating divergent signaling, cell-adhesion, epithelial-mesenchymal transition, DNA replication, angiogenesis, tumor-associated macrophages (Kavalipati et al. 2015; Papanagnou et al. 2017). In experimental studies, different statins showed capabilities to induce apoptosis, cause cytostatic and antiproliferative effects, augment anticarcinogenous properties of standard chemotherapies and attenuate cancer cell migration and invasion. All of the above mentioned properties are of increased importance for potential drug repurposing and use of statins as chemopreventive or adjuvant agents (Papanagnou et al. 2017). Potential and problems and existing gaps in current evidence are related to excessive amount of fragmentary research and data obtained from different models and cancer cell lines, with a lack of direct comparison between different statin molecules.

A systematic review and network meta-analysis by Zhou and colleagues, based on 87,127 patient data from observational studies, indicates that statin treatment is associated with decreased incidence of hepatocellular carcinoma (HCC). Among seven different statins, fluvastatin appeared to provide superior benefit in HCC risk reduction (Zhou et al. 2016). Also, a recent meta-analysis by Yi et al. (2017), demonstrated a statistically significant association between statin use and liver cancer risk reduction. This associated was dose dependent and was observed both in Asian and Caucasian patient subgroups (Yi et al. 2017). Another meta-analysis of 24 studies showed that statin users experienced a significantly decreased risk for developing primary liver cancer, compared with statin non-users, and the risk reduction was more evident in case of rosuvastatin administration. Subgroup analyses revealed greater risk reduction with statins in high-risk patients versus non-high-risk populations (Zhong et al. 2016).

Two recent meta-analyses, involving observational studies assessing statin use and colorectal cancer (CRC) prognosis showed that prescription of statins before and after CRC diagnosis showed a beneficial association between statin use and reduction in all-cause mortality and cancer-specific mortality (Cai et al. 2015; Ling et al. 2015).

In meta-analysis of 7 studies involving 5449 patients with endocrine-related gynecologic cancers, statin use was associated with improved overall survival. Current work also provided evidence on improved disease-specific survival and progression-free survival in statin users with endometrial and ovarian cancers (Xie et al. 2017).

In different pre-clinical studies on breast cancer cell lines, statins have demonstrated a great potential to increase apoptosis, improve radiosensitivity, suppressing cell proliferation, invasion and metastatic dissemination (Van Wyhe et al. 2017). A recent large meta-analysis concluded that use of statins is associated with reduced breast cancer mortality, including both breast cancer-specific and all-cause mortality. Beneficial effects varied in different types of statins – lipophilic statins (lovastatin, simvastatin, fluvastatin, cerivastatin) showed a strong protective function in breast cancer patients, whereas hydrophilic (pravastatin, rosuvastatin, atorvastatin) only slightly improved all-cause mortality (Liu et al. 2017a, b). Another meta-analysis reports improved recurrence-free survival in breast cancer patients, prescribed with lipophilic statins, specifically simvastatin (Manthravadi et al. 2016).

Undoubtely, thoroughly planned studies, assessing perspective placement of statins as adjuvant agents and radio- or chemosensitizers are warranted. Considering lipophilic/hydrophilic properties, targeted efficacy of certain agents against specific cancer types, and preferred duration of exposure might be of substantial importance in oncology.

Antifibrotic Action of Statins

Fibrosis occurring due to chronic tissue inflammation and its retardation under statin use was intensively investigated in patients with liver diseases. Six cohort studies, including 38,951 cases of cirrhosis in 263,573 patients with hepatitis B or C, were included into meta-analysis. Use of statins was associated with a significant 42% reduction in the risk of cirrhosis, being dose-dependent and more pronounced in patients from Asian countries (Wang et al. 2017a, b). Results of another meta-analysis of statin effects in patients with chronic liver disease (CLD) suggest that such drug intervention might delay progression of liver fibrosis and prevent hepatic decompensation in cirrhosis, and reduce all-cause mortality in CLD patients (Kamal et al. 2017). Meta-analysis by Kim et al. (2017) showed that statin use was associated with 46% lower risk of hepatic decompensation and 46% lower mortality in patients with liver cirrhosis. According to data, obtained in RCTs, statin use was associated with 27% lower risk of variceal bleeding or progression of portal hypertension.

Effects of Statins on Renal Function

Apart from benefits in reduction of MACE and all-cause mortality in patients with chronic kidney disease (CKD) (Messow and Isles 2017), statins are continuously reported to reduce the rate of kidney functional decline. Results of meta-analysis evaluating renal outcomes in patients with CKD, demonstrated slower decline of estimated glomerular filtration rate (eGFR) in statin users, compared to controls.

This effect was observed only in case of high-intensity statin treatment; statin intervention did not reduce proteinuria in CKD patients (Sanguankeo et al. 2015). Meta-analysis of data from 11 RCTs, involving 543 diabetic kidney disease patients demonstrated that statins were associated with beneficial reduction of albuminuria, however no influence on eGFR or total proteinuria was observed (Qin et al. 2017). A systematic review and meta-analysis of RCTs from 143,888 non-dialysis CKD patients reports modest reduction in proteinuria and rate of eGFR decline and no benefit in prevention of kidney failure events (Su et al. 2016). Recent survival meta-analysis demonstrated improved patient and graft survival among kidney transplant recipients receiving statins. However, there is still lack of studies evaluating outcomes in renal transplant and dialysis patients or providing head-to-head comparison of different statins (Rostami et al. 2017).

Major limitations of routine statin use as potential anti-aging formula includes the fact that most of the data was obtained from patients at initially high risk of cardiovascular disease or presenting with existing cardiovascular problems. There is still scarce evidence from particularly non-white populations and elderly patients. Long-term outcomes of prolonged treatment, lasting over several decades and its possible risks, remain unknown (Otto 2016).

Problems of Multimorbidity and Polypharmacy in the Elderly: Confounding Effects of Combined Treatment Strategies in Patients with Several Chronic Age-Associated Diseases

Research related to drugs, promoting healthy aging and preventing age-associated diseases and conditions is surrounded by numerous ethical considerations and limitations. For sure, the most desirable setting is life-long use of potential anti-ageing substances in healthy individuals. Assessment of those anti-aging and lifespan-prolonging properties in humans would require a lifetime to determine (Moskalev et al. 2017). Furthermore, as for any type of medications, anti-aging drugs do have side effects, so lifelong prescriptions of those in healthy individuals makes clinical trials unacceptable (Blagosklonny 2009). However, medications which have demonstrated their confident benefits and a reliable safety profile in long-term use, might be potentially evaluated in primary prevention studies. For example, an ongoing RCT STAREE (statins therapy for reducing events in elderly) randomized individuals aged 70 and older without prior cardiovascular disease, dementia, diabetes, or a life-limiting illness to atorvastatin or placebo, with results expected in 2019, will evaluate the role of statins in mortality and functional status (https://clinicaltrials.gov/ct2/show/NCT02099123). The statins are a quite representative group of medications, surrounded by a large number of constraints and considerations regarding prescription in populations of elderly patients. Evidence of statin long-term use in patients aged 75 and older is scarce, due to an insufficient number of

patients having been included into clinical trials (advanced age is often an exclusion criterion) (Leya and Stone 2017); unfortunately, existing data about statin use in people aged 85 and older is insufficient to shape guidelines about rational and safe statin use in this category of patients (Orkaby et al. 2017).

Another complicated aspect of establishing the preventive role of certain agents towards age-associated diseases includes conflicting results, obtained in variable patient populations. A review by Islam et al. (2017) concluded that observational studies, claiming a breast cancer preventive effect of statins could not c establish a certain preventive causal role of these agents. These authors underline the importance of possibly unmeasured confounding variables, having an established effect on risk of cancer, i.e. obesity, physical activity, diet, tobacco and alcohol consumption. Furthermore, there is current discussion that some of the cancer trends in developed countries are a reflection of the wide chronic use of medications with potential chemopreventive properties. Thus, even data from well-designed randomized controlled trials does not consider all of the individual aspects of health and treatment and might not justify certain preventive properties of prescribed agents (Gronich and Rennert 2013).

All of the data about anti-aging properties of certain pharmacologic agents were obtained from large groups of patients, treated for one or more diseases by one certain medication. In these studies confounding and controversial results might be partially explained by multimorbidity of the included patients. So, on one hand, multimorbidity is a desirable inclusion criteria, because aging is accompanied by a number of health-deteriorating conditions and it is necessary to evaluate potential effects of certain medication on several conditions (i.e. improvement of survival of T2DM patients with certain cancers in case of chronic metformin use). On the other hand, multimorbidity is a synonym of multiple medication prescription, when it is impossible to assess individual action of each substance per se, thus providing researchers with confounding and inconclusive data (Fabbri et al. 2015). Many chronic conditions in elderly patients require combined treatment strategies and the use of polypill strategies, improving compliance and outcome is nowadays not rare (Hedner et al. 2016; Lafeber et al. 2016). This problem is especially large in population of elderly patients, as different studies show that more than one third of elderly patients are receiving five and more prescription drugs at once, which is often accompanied by intake of one or more over the counter drugs or dietary supplements (Maher et al. 2014).

Study by Johanna Jyrkka and colleagues established that excessive polypharmacy in elderly patients, aged 80 years and over, defined as concomitant consumption of ten and more prescription medications is an indicator of 5-year mortality (Jyrkkä et al. 2009). This issue might be addressed by the fact that certain medications with anti-aging properties affect several disease at once, thus clustering of several diseases with common underlying pathophysiological mechanisms into triades or groups might be beneficial for research and clinical practice (Schäfer et al. 2014; Violan et al. 2014).

A Cochrane review by Smith et al. (2016) underlines the fact that there is still lack of solid definitions for multimorbidity and related concepts such as comorbidity,

complexity, frailty, and vulnerability. This leads to misclassification of patients, especially when considering the heterogeneity of multimorbidity, and might provide false conclusions about the effects of intervention. RCTs often include age and concomitant disease limitations, which does not allow clinicians to precisely depict the whole spectrum of effects for potential anti-aging substances (Zulman et al. 2011). Studies evaluating drug effects in chronic anti-aging agent users could also be biased by self-reporting of patients, often experiencing cognitive decline, lack of compliance due to the cost of treatment or just partial adherence to recommendations (Yap et al. 2016).

Additionally, the population of older adults has a long story of inconsistent prescription patterns, including under-prescription of certain agents with side effects (i.e. statins) (Orkaby et al. 2017). Clinicians often hesitate to use drug with known side effects, being additionally concerned about potential drug-drug interactions, which have essentially not been studied in elderly individuals (Strandberg et al. 2014).

Some life-span prolonging agents, affecting various pro-aging targets, often demonstrate controversial or negative results when tested in vivo. An appropriate example of this phenomenon is co called "antioxidant paradox": reactive oxygen species and oxygen radicals are involved into process of aging and pathogenesis of age-related diseases, however dietary supplementation with large doses of antioxidants have no preventive or therapeutic effect. Biswas (2016) underlined the fact that unsuccessful attempts to reduce oxidative stress in humans by antioxidant supplementation is partially explained by lack of reliable biomarkers, which could be used to measure redox status in humans. On the other hand, preferential targeting of ROS is possibly harmful, especially in case of cancer, when ROS production plays an important role in malignant cell apoptosis induction (Biswas 2016). Still, many of the crucial mechanisms of aging remain undiscovered and untargeted, and selective targeted of ROS, with very limited or nearly no success, is a good demonstration of our limited knowledge in this field (Halliwell 2013).

Another translational problem is based on the fact that we still do not have reliable biomarkers of aging, easily assessable in patients and allowing one to draw conclusions about the definitive anti-aging effect of intervention (Blagosklonny 2009; Moskalev et al. 2016). Basically, available clinically relevant evidence from clinical trials is based on the outcome of certain age-related disease prevention treatments, when their onset and progression had already happened, and not on the earlier markers of aging and age-related functional decline itself.

Conclusions and Perspectives

Because of their widespread used as medications, some FDA approved drugs are effective to prolong both life- and healthspan. Their effects are mostly associated with triggering the pathways shown to regulate lifespan in various experimental models. Unfortunately, many drugs were effective only in worms and flies and

much less in rodents. The reason for this phenomenon is their differences in physiology and additional factors not taken into account. However, the use of combined treatments with an already beneficial compound may give significant steps forward, leading to the extension of human lifespan and decreasing age-related pathologies.

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