Potential of nanoparticles and nanopolymers in treatment of age-associated diseases

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Abstract

Aging is an inevitable process caused by the accumulation of degenerative destructions, which ultimately leads to organism death. As the aging process occurs at the molecular, cellular, and tissue levels, understanding the whole details is the prerequisite for the development of anti-aging therapy. More than 300 compounds of different sources have been reported with the anti-aging activity that slow aging and extend lifespan through regulating single or multiple signaling pathways. Recent innovations in nanotechniques could lead to the development of nanomaterials having anti-aging effects or acting as nanocarrier systems and distributers of anti-aging drugs. In this review, we summarized the molecular mechanisms of longevity and the prospect of developing anti-aging nanomaterials targeting aging pathways.

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Abstract

Aging is an inevitable process caused by the accumulation of degenerative destructions, which ultimately leads to organism death. As the aging process occurs at the molecular, cellular, and tissue levels, understanding the whole details is the prerequisite for the development of anti-aging therapy. More than 300 compounds of different sources have been reported with the anti-aging activity that slow aging and extend lifespan through regulating single or multiple signaling pathways. Recent innovations in nanotechniques could lead to the development of nanomaterials having anti-aging effects or acting as nanocarrier systems and distributers of anti-aging drugs. In this review, we summarized the molecular mechanisms of longevity and the prospect of developing anti-aging nanomaterials targeting aging pathways.

keywords

Aging; Nanomaterial; Biomolecule stability; Drug Discovery; Pharmaceutical bioassays

The age-related diseases

The improvement of the environment, nutrients, medical assistance, and also reducing the prevalence of infectious diseases has resulted in a rapid increase in life expectancies and overall age increasing in industrialized and developing countries (Passarino, De Rango, & Montesanto, 2016). Reportedly, the average life expectancy increased in the early 21st century to above 65 years as compared with 35 years in the 18th century (Pan, Lai, Tsai, Wu, & Ho, 2012). Based on statistics, 2 out of the 9 billion people in 2050 will have been at least six decades (Kennedy & Pennypacker, 2014), and it seems that this increasing trend in lifespan may be one of the major risk factors in the aging-associated diseases. The increasing age of individuals is associated with a rise in a multitude of multiple chronic diseases that contributes to a global disease burden and mortality (Aburto, Villavicencio, Basellini, Kjærgaard, & Vaupel, 2020). Autoimmune diseases, diabetes, cardiovascular disease, hypertension, arthritis, different types of cancers, asthma, osteoporosis and skeletal disorders, dementia and neurodegenerative damages, such as Parkinson, Alzheimer, Huntington's disease and amyotrophic lateral sclerosis are among common aging-associated diseases (López-Otín, Blasco, Partridge, Serrano, & Kroemer, 2013) Aging is assumed as a progressive and ineradicable complex process, resulting from an accumulation of various damages that origin from malfunctions in maintaining the cellular pathways (Niccoli & Partridge, 2012). Revealing the mechanisms that aging enhances the risk of the dysfunction disease needs further investigation in the complex networks of molecular and cellular interactions in model organisms and ultimately in humans. In **Table 1** , several cellular and molecular factors associated with aging playing a conspicuous role in the progression of age-related disorders are presented.

TABLE 1

Mechanisms of aging at the molecular, cellular, and tissue levels

Considering that aging is the major risk factor for age-associated diseases, discovering the molecular processes of aging is extremely critical for maintaining the health of communities and individuals. In-depth researches throughout the years have increased the knowledge about \souton aging that incorporated various assessments, such as metabolomics, proteomics, transcriptomics, detection of the macromolecular damages, and induction of stress response pathways, which are linked to the aging and age-associated diseases (**Figure 1**)(Russo et al., 2020). Maintenance of telomere biology, DNA repair, antioxidant mechanism, detoxification, autophagy, protein unfolding response, and proteasome protein degradation are crucial mechanisms that promote maintenance of genome stability, metabolic homeostasis, proteostasis, ultimate cellular and organismal function, and survival. The inefficacy of these restoration processes can trigger the incidence of aging and its consequent pathogenesis while boosting the protection processes postpone the process of aging and its associated damages. Thus, inhibition of their failure or improvement of their efficiency can be inspired for the design of the screening platform for anti-aging compounds resources (López-Otín et al., 2013).

Nanotechnology, the most forthcoming technology of the twenty-first century, is a remarkable part of science that covers the design, production, characterization, and application of materials, tools, and systems at the nanoscale (Romig Jr et al., 2007). The nanotechnology application in different aspects of medicine provides opportunities to investigate the biological systems at the subtlest levels, causing a higher perception of the mechanisms behind the diseases. In addition, it provides tools for more precise and real-time diagnoses of diseases, targeted drug delivery, new approaches in various kinds of tissue regeneration (Luxenhofer, Barz, & Schillmeier, 2014).

FIGURE 1

Nanomedicine combines nanotechnology with different fields of study, including materials science, medicine, engineering, cellular and molecular biology, medical sciences and pharmacy, and computational technology. And they are considered as incorporated nanoparticle\souts drugs or biologics (1-100s nm) to provide either enhanced targeting, diminished toxicity, or otherwise augmented efficacy of imaging or therapeutic (B. Y. Kim, Rutka, & Chan, 2010). The interactions of nanomaterials with biological targets (at the level of molecules, cells, organs, etc.) are dependent on complex interactions between the adjustable attributes of the particles and the largely irrepressible attributes of the circumambient media. The physical characteristics of the nanomaterials, such as size and shape of particles as well as their functional groups are key factors that

influence the parameter of their performance such as the cellular uptake, the degree of protein adsorption, biodistribution patterns or the mechanisms of their clearance (Nel et al., 2009; Pelaz et al., 2017).

The current nanodrugs are mainly involved in the enhanced permeability and retention effect (Maeda, 2015). The nanomaterials generally enhance their accumulation in ischemic tissue, or inflamed organ by adsorption of their specific surface ligands, such as aptamer, antigen, protein, etc. (Albanese, Tang, & Chan, 2012). Modifications in some parameters, including pH (Sato, Yoshida, Takahashi, & Anzai, 2011), temperature (Jun-Hyun Kim & Lee, 2004), the addition of certain enzymes (De La Rica, Aili, & Stevens, 2012), and redox potential (Luo et al., 2011) can be used to adjust the controlled release of these types of drugs. Moreover, nanomedicines are able to bypass membranes or even the blood-brain barrier and allow the distribution of drugs to the target tissue at high concentrations. The knowledge of nanodrugs application in medicine\sout, creates novel approaches in developing implantable materials, directed diagnosis, and therapeutic for the treatment of cancer, wound healing, etc.

Nanoparticles and nanopolymers with Anti-aging activity

Since the past years, several nanoparticles have been synthesized using different ingredients. Dissolving, encapsulation by an association of the desired drugs to the various nanoparticles made of metal salts, proteins, lipids, polysaccharides, and synthetic polymers can improve the process of treatment of various diseases, including aging-related diseases.

Three generations of nanoparticles, including nanosphere (a matrix formed by a polymer), nanocapsule (a vesicle consists of a soluble drug in a liquid), and targeted nanoparticle (ligands-decorated colloidal system) have the potentials to be applied in nanomedicine.

The three-dimensional structure of the nanodrug, the extent of drug distribution, and its amount of immune response induction can be influenced by the size, shape, physicochemical characteristics, and surface properties adjusted for their synthesis. Currently, nanodrugs in clinical use, which are approved by the FDA reach more than 50, and also more than 77 nano-based are being examined in Phase I and III of clinical trials (Bobo, Robinson, Islam, Thurecht, & Corrie, 2016). However, only a limited number of these drugs have been introduced as a direct target of aging, and many are used as treatments for aging-related diseases. Some anti-aging nano drugs approved by the FDA are listed in **Table 2** .

TABLE 2

Aging targets of nanomedicines at the molecular level

Genome stabilizing nanomaterials

The human genome is constantly exposed to different kinds of mutagens (externally imposed chemical, physical and biological determinants), and endogenous factors, especially genome replication errors, produced reactive oxygen species and spontaneous hydrolytic reactions (Zid et al.). Also, somatic mutations, such as aging-related mitochondrial DNA (mtDNA) mutation, could alter the stability and integrity of genomic DNA (C. B. Park & Larsson, 2011). The accumulation of mutations and damages with time may lead to genetic instability and could impact transcriptional pathways and gene functionality. These processes could alter cells function and induce a disturbance in tissue and organismal homeostasis, leading to age-associated disorders, such as carcinogenesis, neurodegenerative diseases, and some premature aging disorders such as Werner syndrome and Bloom syndrome (Burtner & Kennedy, 2010; Moskalev et al., 2013). On the other hand, various forms of epigenetic changes and microsatellite instability, including\sout, modification of histone, methylation of DNA, and mutation of microRNA and telomere shortening, have a reverse effect on the stability of the human genome. Several diseases caused by aging like cancer, atherosclerosis, diabetes, neurodegenerative complications, and immune response deficiency are associated with epigenetic disorders (Calvanese, Lara, Kahn, & Fraga, 2009). Furthermore, telomere dysfunction and consequent genomic instability have a critical influence on aging at a cellular level involved in the induction of senescence or apoptosis that might contribute to age-related diseases (Innan, Veitia, & Govindaraju, 2020). Having knowledge of signaling mechanisms

associated with DNA stability and mtDNA integrity may help us to delay aging and potentially reduce the incidence of many genomic related disorders (Blackburn, Greider, & Szostak, 2006).

The metal nanoparticles can induce genotoxicity and mutagenicity by exposure to the genome or damaging the mitotic separation and its structural components (Kumar & Dhawan, 2013), in contrary, some nanoparticles can be used in delivering the nucleic materials (i.e., DNA, RNA, and siRNA) and oligonucleotides (including genes). The modification of genetic materials has been reported in various chronic disorders (Rea et al., 2018). Gene therapy using nanomedicine need preliminary detection of the genetic disorders in targeted cells. The composite nanoparticle can alter the pattern of transcription and translation of genes leading to modulation of gene functions through genetic manipulation in targeted tissue (Shajari, Mansoori, Davudian, Mohammadi, & Baradaran, 2017).

According to illumined molecular mechanisms of age-related complications, nanomedicine may be a potent future tool in the development of appropriate medications for age-associated genetic malfunctions via gene manipulation approaches.

Protein degradation inhibition by Nanomaterials

The lysosome–autophagy system and the ubiquitin-proteasome system (UPS) are the well-known mechanisms for removing the modified and aggregated proteins, and damaged organelles as cellular wastes. The cooperative function of autophagy and UPS systems function produce short-chain polypeptides that maintain the amino acid supply and energy balance of the starved cells, which is vital in maintaining the cellular homeostasis (Mizushima, Levine, Cuervo, & Klionsky, 2008; Nam, Han, Devkota, & Lee, 2017). It is shown that the diminished rate of intracellular protein degradation and autophagy, led to the misfolded proteins and non-functional macromolecules inside the cell, which are involved in the pathology of neurodegenerative disease associated with aging, such as Parkinson and Alzheimer (Jiang & Mizushima, 2014; Nah et al., 2015). Also, the dysregulated autophagy system impact on the innate immune response. Pro-inflammatory factors activity, cytokine/chemokine secretion, lymphocyte activity, and tracing antigen were associated with blunted autophagy response in some age-related diseases (Cuervo & Macian, 2014; Shi et al., 2012).

More than forty types of nanomaterials have been reported so far with modulating effect on cell autophagy, including diverse structural types of graphene, carbon-based nanotubes, gold particles, dendrimers, iron oxide, cationic liposomes, fullerene and its derivatives, silica, and ∝-alumina (Cordani & Somoza, 2019). Nanomaterials can influence the process of cell autophagy via multiple pathways. These compounds can have plausible applications in the detection and control of autophagy-associated diseases, especially those related to aging. Different nanomaterials mediate distinct mechanisms of autophagy based on their disparate chemical and physical particularity (Wei & Le, 2019). The mechanisms of autophagy modulation induced by nanomaterials can be categorized into three classes: oxidative stress induction, direct regulation of autophagic signaling pathways, such as Akt/mTOR, and alteration of the autophagy-related genes or proteins expression level (Zheng, Wei, Li, & Le, 2016).**Table 3** summarizes some nanomaterials with autophagic modulating modulatory effects as anti-aging materials.

TABLE 3

Cellular targets of nanomedicines

Regulatory effect of nanoparticles on Endoplasmic Reticulum (ER)

The endoplasmic reticulum is a cellular compartment involved in protein folding and maturation (Zid et al.). It is particularly involved in the suppression of protein aggregation through multiple levels by maintaining the accuracy of accurate transcription of DNA to RNA and then the translation of RNA to proteins as well as chaperons of nascent and unfolded proteins (Ellgaard, Molinari, & Helenius, 1999).

The main limiting stage in the biogenesis of both transmembrane or secretory proteins is the folding process in the ER. The chaperones and folding enzymes are responsible for different stages of quality control and protein folding processes (Naidoo & Brown, 2012). The reduced efficacy of chaperones and foldases by

aging lead to the cumulation of abnormal proteins in the ER and finally trigger the activation of unfolded protein response, which is related to ER-stress (Berridge, 2002). This triggers some of the protective cellular responses, including the up-regulation of some chaperones to promote the restoration of protein structures, proteolysis of misfolded proteins, and attenuation of protein translation (Brown & Naidoo, 2010).

By increasing the age, the potency of processing the abnormal proteins decreases following the diminished components of the ER stress and UPR tools. This inefficient protein refolding process leads to age-associated disorders, such as neurodegenerative deteriorations, vascular inflammation, atherosclerosis, and a variety of cancer diseases (Forman, Lee, & Trojanowski, 2003; Johnson et al., 2008).

Drugs or nanomaterials can alleviate the ER stress through improving the accurate folding of proteins, modulating the efficiency of ER-related degradation, and increasing the recognition of misfolded proteins that may lead to the prevention of age-related diseases and disorders (Naidoo & Brown, 2012). There has been no report of nanoparticle stress inhibition in the ER with the aim of delaying or treating aging. Therefore, it can be considered as a new research target for this purpose.

Regulation of Mitochondrial activity by nanoparticles

It has been confirmed that aging and the age-dependent reduction in organ function are associated with a decline in mitochondrial operation (Rockstein & Brandt, 1963). Mitochondrial mutations leaging to functional irregularity in the processes related to the functioning of this organ in all tissues (**Table 4**) (Cortopassi, Shibata, Soong, & Arnheim, 1992).

In humans, the mitochondrial malfunction is related to the aging process and can predispose humans to some age-related diseases when they reached a significant enough level (Khrapko & Vijg, 2009). Thus, aging is implicated by a decrease in the activity of mitochondrial components, such as mitochondrial enzymes, particularly citrate synthase, a reduction in respiratory capacity per mitochondria, an increase in production of ROS (Zid et al.), and a reduced phosphocreatine (PCr) recovery time (Sun, Youle, & Finkel, 2016).

TABLE 4

Apoptosis inhibitors and regenerative nanomedicines

Senescence can be considered a stress response intensified by genomic damages, nucleotide mutations, telomere attrition, protein aggregation or misfolding, and oxidative damage causing or initiating the age-related diseases. Moreover, senescent cells can participate in the induction of pro-inflammatory phenotype (Campisi, 2013; Childs, Durik, Baker, & Van Deursen, 2015; McHugh & Gil, 2018; Muñoz-Espín et al., 2013; Serrano, 2014). The production of pro-inflammatory agents and suppression of cell proliferation are two important hallmarks of senescence response that alter the intracellular and intercellular communications (Childs et al., 2015). The findings have shown a complex correlation between senescent cells, apoptosis, and mitochondrial malfunction with increased age (Sun et al., 2016). Studies on mice and human models have confirmed the accumulation of the senescence biomarkers in tissues, which are associated particularly with atherosclerosis, cancer, rheumatoid arthritis (RA), and neurodegenerative disorders (Campisi, Andersen, Kapahi, & Melov, 2011; Erusalimsky & Kurz, 2005; Krizhanovsky et al., 2008).

Nanomaterials can be functionalized with ligands, immunoglobulins, or polymers for selective targeting of senescent cells which can be used for therapeutic purposes in addition to diagnostic applications. Besides, the capability of the nanomaterials in detection of cancer cells or induction of apoptosis, some nanomaterials are known in regenerative medicine. Moreover, they can have a determinant role in the restoration of aged, disturbed, damaged, or even lost cells resembling their original structure and function. Additionally, these materials can have the extra potential to diminish the disadvantageous phenotype of the aged cell by modulating the senescence-associated secretory phenotype (SASP) (Salminen, Kauppinen, & Kaarniranta). They can maintain tissue-associated functions with encapsulated inhibitors, small molecules, and effectors, or by reprogramming these cells (Muñoz-Espín, 2019). The progress in nanotechnologies and nanomedicines to treat the senescent cells as anti-aging agents is however still in its infancy, and since the toxicity of many of them has been proven, the important limitation in their application is accompanied by the concern of their

safety for human and environment. Some of the nano-compounds that are shown effectivity in inhibiting apoptosis or cells regenerating are listed in **Table 5** .

TABLE 5

Aging postponing nanoparticles at the tissue level

Nanomaterial with anti-inflammatory activity

Despite many studies on factors and pathways affecting human aging, the molecular mechanisms that link the process of aging to diseases have not been systematically explored (Dimmeler & Nicotera, 2013). Recent evidence reflects that the pro-inflammatory gene induction and related inflammatory pathways activation are critical causative triggers in aging and several age-related diseases (Chung, Sung, Jung, Zou, & Yu, 2006). Many studies confirmed the direct link between inflammatory pathways and aging. Based on this hypothesis, redox stress leads to age-associated alterations. This imbalance of cellular redox is incorporated by the immune system perturbation, hormonal changes, and also modifications on a cell's DNA or histones and gene expression subsequently as well as telomere shortening contributes to elevated inflammation in aging (Fougère, Boulanger, Nourhashémi, Guyonnet, & Cesari, 2016).

Based on *in vitro* and *in vivo* studies on senescence state, the increased generation of some of the important pro-inflammatory proteins, such as COX-derived RS is confirmed and also elevated expressions of TNF-α, IL-1b, IL-6, genes, COX-2, iNOS, and others like AMs (VCAM-1, ICAM-1, P-, E-selectin) are also have been detected (Chien et al., 2011; Chung et al., 2009, Chung, 2011). Studies on human models have illustrated that aging is associated with incremental levels of IL-6, IL-1, TNF-a, CRP in plasma accompanied by high numbers of inflammatory cells (neutrophil, monocytes) (Bruunsgaard, 2006). According to the recent medical investigations, chronic systemic inflammation has a central and remarkable role in the initiation and progression of the age-dependent complications (**Figure 2**), such as dementia, atherosclerosis, metabolic syndrome, cancers, osteoporosis, sarcopenia, etc. (Olivieri, Rippo, Procopio, & Fazioli, 2013). Although each disease is characterized by various inflammatory molecular factors, the fundamental mechanisms of the pro-inflammatory mediated process, including cytokines, chemokines, and other signaling molecules, are rather identical (Chung et al., 2009).

The current anti-inflammatory drugs mainly have steroidal structures, such as prednisone, betamethasone, and dexamethasone, while non-steroidal anti-inflammatory medications have shown lower efficacy, such as aspirin, ibuprofen, and naproxen (Ghlichloo & Gerriets, 2019).

FIGURE 2

The nanotechnology provides extensive and effective nanomaterials and tools that could be used in the detection and treatment of different inflammatory disorders and conditions. Some *in vitro* and*in vivo* experiments have been performed to examine the impact of nanoparticles on the development of inflammation and its subsequent disorders (Kadhim, Karsh, & Jabir, 2020). By modulating the nanoparticles, they can be directed to pass from the metabolic barriers and deliver drugs to particular targets without interacting with other cells. This makes them promising therapeutical candidates as anti-aging drugs that exert their effect by limiting the local inflammation.

In spite of the therapeutic potential of bioactive nanoparticles in the treatment of diseases initiated by chronic inflammation, still, further studies are required to overcome their potential toxicity and identify their pharmacokinetic properties, such as the least effective concentrations, physicochemical interactions, route of administration, etc. (Elsayed & Norredin, 2019). New advances in nanotechnology and nanomedicine-based strategies have led to the emergence of nanomedicine for the inflammatory disease treatments that can be directly effective in delaying aging (**Table 6**) (Rizzuto et al., 2019).

TABLE 6

Conclusion and future perspective

An increase in life expectancy is the result of public health initiatives and successful infection control interventions. Reports indicate that 8 million people have been added to the world's elderly population each year, and this increase will reach 24 million per year by 2030 (Nikolich-ugich et al., 2016).

At the molecular scale, aging is a result of collective damages to the biomolecular systems over a time span that could lead to various organ injury and physical and mental and subsequently contribute to age-related diseases that can impose high costs on the medical systems. Therefore, efforts to achieve treatment and medication methods that can prevent the disorders by targeting aging pathways will be worthwhile and valuable.

Consecutive to the advances in next-generation technologies, transcriptomic and proteomic, multiple genes involved in aging and longevity have been recognized in diverse organisms that disclose potential targets for designing novel anti-aging drugs. With the continued development of high-throughput screening (HTS) technologies and their application by pharmaceutical companies, enormous clinical medicines with a variety of therapeutic purposes are obtained from nanomaterials and their derivatives. Nanotechnology, along with chemical drugs and, in some cases, drugs of natural origin, has become very popular over the past ten years. Nanomaterials are widely used in the production of anti-aging skin medications in many cosmetics. Nanomedicines could act by directly modulating various signaling pathways, and function as anti-inflammatory, anti-apoptotic, autophagy regulatory, and genomic stabilizer compounds effect on aging progressing (Lin-Ping, Wang, & Li, 2019).

Nevertheless, it is evident that the evaluation of the anti-aging potential of nano-based compounds must include some pivotal assessments to mitigate the concerns on toxicity, modes of functions, interacting targets/pathways, effective and optimum dosage, clearance from the body, and finally, reproducibility and predictability of the interactions.

It is anticipated that the advancement in revealing the genetic and epigenetic molecular process of aging, along with the significant improvement in designing the safe nanomaterial, cooperatively can translate to a more reliable nano-based agent to fortify the longevity of human species.

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Authors declare no conflict of interest for the content of this review paper.

Authors' contributions

FS: data collection and writing the draft; FM: Conceptualization and manuscript edition; NZ: Writing part of the draft; MH: Manuscript edition

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Table 1 Main mechanisms/pathways initiating the development of age-related diseases. Abbreviations: IIS (Insulin/insulin-like growth factor-1 (IGF-1) signaling), TOR (Target-of-rapamycin(, MAPK (5' adenosine monophosphate-activated protein kinase), CRP (C-reactive protein), PDs (Parkinson's disease), ROS (Reactive oxygen species), DDR (DNA damage response), RANKL (Receptor activator of nuclear factor-ϰB ligand)

Diseases	**Effector mechanisms mediating the age-associated disorders**	**Effector mechanisms mediating the age-associated disorders**	**Effector mechanisms mediating the age-associated disorders**	**Effector mechanisms mediating the age-associated disorders**	**Effector mechanisms mediating the age-associated disorders**
	IIS/TOR signaling and AMPK	**Mitochondrial dysfunction**	**Genomic damage and telomere degradation**	**Autophagy Defection**	**Inflammation response**

Diseases	Effector mechanisms mediating the age-associated disorders	Effector mechanisms mediating the age-associated disorders	Effector mechanisms mediating the age-associated disorders	Effector mechanisms mediating the age-associated disorders	Effector mechanisms mediating the age-associated disorders
Cardiovascular	Resistance to Insulin can cause abnormality function in the cardiac system (S.-Y. Park et al., 2005) Downregulation of insulin, TOR and AMPK can prevent cardiovascular disease (Hernández et al., 2011)	Defective mitochondria lead to cardiomyocyte apoptosis (Crow, Mani, Nam, & Kitsis, 2004)	Induce endothelial senescence leading to atherosclerosis (Minamino & Komuro, 2002)	Autophagy failure can stimulate Cardiomyopathy and cardiac hypertrophy (Fidziańska, Bilińska, Walczak, Witkowski, & Chojnowska, 2010)	CRP and fibrinogen rise in plasma can lead to cardiovascular disorders (Coppola et al., 2006)
Neurodegenerative	Longevous IIS mutants as well as decreasing of IIS signaling can play a role in some nervous system dysfunction (Broughton & Partridge, 2009; O'Neill, Kiely, Coakley, Manning, & Long-Smith, 2012)	Impairment in function ais associated and promote pathology, especially in PDs (Moon & Paek, 2015)	Neuron death related to damaging DNA structure has a role in neurode-generative diseases (Kruman et al., 2004). Telomere engaging is unknown	Accumulation of toxic proteins due to autophagy flaw can associate with neuropathology (Fang, Gu, Smerin, Mao, & Xiong, 2017; Nixon & Yang, 2011; Schöndorf et al., 2014)	Reducing in brain size seen due to increased amount of IL-6, TNF-α, and CRP in plasma (Ishikawa, Kobayashi, Fujii, & Kobayashi, 2015; Tan et al., 2007)
Type II Diabetes	IIS inhibition in peripheral tissues, leading to insulin resistance associated with the pathology of diabetes (Ohshima et al., 2012)	Oxidative stress and mitochondrial dysfunction (M Victor, Rocha, Herance, & Hernandez-Mijares, 2011), decline ATP production leading to insulin resistance (Veech, 2004)	There is a direct association between oxidative DNA damage and the complications of diabetes (Hinokio et al., 1999)	Defects in autophagy lead to pancreatic beta cell dysfunction (Marchetti & Masini, 2009), insulin resistance and accumulation of toxic molecules (Yang, Li, Fu, Calay, & Hotamisligil, 2010)	the higher levels of pro inflammatory cytokines, IL-6, TNF-α, and CRP can increase insulin resistance (Mirza et al., 2012)

Diseases	Effector mechanisms mediating the age-associated disorders	Effector mechanisms mediating the age-associated disorders	Effector mechanisms mediating the age-associated disorders	Effector mechanisms mediating the age-associated disorders	Effector mechanisms mediating the age-associated disorders
Cancers	Downregulation of IIS and TOR signaling suppresses tumors (Partridge, Alic, Bjedov, & Piper, 2011)	Mutation in mtDNA and an increase in mitochondrial ROS are oncogenic factors (H.-C. Lee, Chang, & Chi, 2010)	Rambunctious growth as well as accumulated numerous mutations in cancer cells can be caused by DDR defects (Menendez et al., 2011), Telomere shortening could be related to senescence of tumor suppressor (Bruunsgaard, Pedersen, & Pedersen)	Autophagy protects initial steps of tumor growth and makes cancer cells spread (Pavlides et al., 2012)	TNF-α, IL-6 and cyclooxygenase play a key role (Willcox et al.)
Rheumatoid Arthritis	TOR signaling inhibition has a protective effect (Malemud, 2015)	Leaks in the respiratory chain create ROS and lead to atherosclerosis by multiple pathways (Hulsmans, Van Dooren, & Holvoet, 2012)	A decrease in DDR may be related to disease progresses (S.-H. Lee et al., 2003)	A defect in lysosomal degradation system (autophagy) or ubiquitin–proteasomal regulation causes joint inflammatory disorders (N.-Y. Lin et al., 2013)	Antigen-specific immune responses by T-lymphocyte, Cytokine signaling network(T-cell-independent), and invasive function like a tumor play roles in this disease (Phillips, Dias, Kitas, & Griffiths, 2010)

Diseases	Effector mechanisms mediating the age-associated disorders	Effector mechanisms mediating the age-associated disorders	Effector mechanisms mediating the age-associated disorders	Effector mechanisms mediating the age-associated disorders	Effector mechanisms mediating the age-associated disorders
Sarcopenia	yperactivation of mTOR leads to skeletal muscle fibers damage in aged people (H. Tang et al., 2019), up-regulated MAPK signaling contributing to the impaired regeneration a (Carlson et al., 2009)	Oxidative stress, altered mitochondrial dynamics, change in mitochondrial turnover and induce mitochondrion-mediated apoptosis (Derbré, Gratas-Delamarche, Gómez-Cabrera, & Viña, 2014)	-	Accumulation of toxic proteins due to autophagy defects can cause the pathology (Masiero & Sandri, 2010)	An increased amount of TNF-α, IL-6, and also CRP in plasma enhances problems in muscle mass, strength, and catabolism (Schaap, Pluijm, Deeg, & Visser, 2006)
Osteoporosis	Over-active osteoclasts (TOR-dependent) cause osteoporosis (Blagosklonny, 2008)	mtDNA deletions and mitochondrial ROS promot pathology (Abdollahi, Larijani, Rahimi, & Salari, 2005)	An increase in IL-6, TNFα, and RANKL by persistent cellular DNA damage (Blair & Athanasou, 2004)	Decreased autophagic activity in osteocytes (Blair & Athanasou, 2004) and increase apoptosis of mature osteoblasts and osteocytes	High levels of some interleukins (1,6,11,15 and 17) and TNF-α have key roles in pathology progression (Mundy, 2007)

Table 2 FDA approved nanomaterial-based Anti-Aging compounds

Drug	Composition	Age-Related Indication
Doxil/Caelyx	PEGylated liposomal formulation of doxorubicin	Various Cancers
Ontak	Denileukin diftitox	Cutaneous T-cell lymphoma
Visudyne	liposomal formulation of verteporfin	Wet age-related macular degeneration
Eligard	Leuprolide acetate and PLGH polymer formulation	Advanced prostate cancer
Estrasorb	Micellar Estradiol	Vasomotor symptoms in Menopause
Macugen	PEG-anti-VEGF aptamer	Neovascular age-related macular degeneration as a c
Abraxane®	Albumin-bound paclitaxelnanoparticles	Breast Cancer
Renvela	Sevelamer carbonate; and Sevelamer HCl	Chronic kidney disease
Cimzia®	Certolizumab pegol	Rheumatoid arthritis
Abraxane®	Albumin-bound paclitaxelnanoparticles	Pancreatic Cancer
Onivyde®	Liposomal Irinotecan	Pancreatic Cancer
Zilretta	Triamcinolone acetonide	Osteoarthritis knee pain

Table 3 Known nanomaterials with autophagy modulatory activity

Nanoparticles	Model of study	Targeted protein/signaling	Observed
Fullerene C60	HeLa; MEF; MCF-7	Atg5	Autophag
Single-walled carbon nanotubes	Primary glia from CRND8 AD murine	mTOR-S6K	Autophag
Graphene oxide	HeLa; GFP-Htt(Q74)/PC12	PtdIns3K and MEK/ERK1/2	Activation
Silver nanoparticles	Primary MEF; Hela	PtdIns3K	Autophag
Iron oxide	A549; IMR-90	Akt-AMPK-mTOR	Selective i
Bismuth nanoparticles	HEK293	AMPK/mTOR	Autophag

Table 4 Nanomaterials with radical scavenging activity or as the carrier of the antioxidant compounds

Nanomaterial	Aging-related disease	Model	Reference
Platinum nanoparticles (nano-Pt)	Aging	*C. elegans*	(J. Kim et al., 2008)
Dicetyl phosphate--modified negative solid lipid nanoparticle (DCPmod-SLN) system	Aging skin	Mouse	(Jeon et al., 2013)
Gold nanoparticles (GNPs)	Aging skin	Collagen lattice model	(Ji-hoon Kim, Hong, Koo, Choi, & Lee, 2012)
Cerium(Zid et al.) oxide (CeO2) NPs	Cerebral ischemia	Mouse	(Sandhir, Yadav, Sunkaria, & Singhal, 2015)
Yttrium oxide (Y2O3)	Diabetes	Rat	(Ghaznavi et al., 2015)
Curcumin loaded-PLGA (poly (lactic-co-glycolic acid))-tet1 NPs	Alzheimer's disease	Mouse	(Sandhir et al., 2015)
Quercetin in polylactide nanocapsule		Rat	(Zhang et al., 2009)

Age-related cerebral oxidative injury

Nanomaterial	Aging-related disease	Model	Reference
Epigallocatechin gallate in nanolipid particle	**Neurodegenerative diseases including Alzheimer's and Parkinson diseases**	Mouse Gerbil	(Sandhir et al., 2015)
Resveratrol- loaded polysorbate 80-coated poly(lactide) NPs have	**Parkinson**	Mouse	(Sandhir et al., 2015)
Resveratrol-loaded lipid-core nanocapsules	**Alzheimer's diseases and decreasing in tumor size**	Rat	(Sandhir et al., 2015)
Tween 80-coated chitosan NPs of gallic acid showed	**Scopolamine-induced amnesia**	Mouse	(Sandhir et al., 2015)
Sesamol-loaded solid lipid NPs	**Menopause-related implications** **Cognitive CNS derangements in ovariectomy**	Rat	(Sandhir et al., 2015)

Nanomaterial	Aging-related disease	Model	Reference
Superoxide dismutase polyethyleneimine-poly (ethylene glycol) (PEIPEG)	**Parkinson**	Mouse	(Sandhir et al., 2015)
Trolox or polyphenols conjugated to gold NPs	**Neurodegenerative disorders**	*In vitro*	(Sandhir et al., 2015)
Tempol-loaded poly-(lactide-co-glycolide) (PLGA) NPs-transferrin	**Alzheimer's and Parkinson diseases**	Rat	(Sandhir et al., 2015)
Q10, retinyl palmitate, tocopheryl acetate, grape seed oil, and linseed oil loaded on NPs	**Skin wrinkles**	Volunteer humans	(Felippi et al., 2012)
Epigallocatechin-3-gallate (EGCG) and hyaluronic acid loaded nano-transfersomes	**UV-induced skin damage**	Rat	(Avadhani et al., 2017)

Table 5 Nanostructures inhibiting the cell senescence or inducing cell regeneration

Nano -structure	Molecular effect	Anti-ageing iological funtion	Reference
CD9-Lac/ $CaCO_3$	Downregulation of some SASP components, including IL-6 and IL-1b	**Anti-senescence effects on primary human dermal fibroblasts (HDFs)**	(Thapa et al., 2017)
MoS_2	Inhibition of H_2O_2-induced senescence by preventing lysosomal and mitochondrial dysfunction, triggering autophagy	**Anti-senescence effects on endothelial functions**	(Ke et al., 2018)
Poly(lactic-co-glycolic acid) (PLGA) surfaces	Adhesion to chondrocyte and proliferation	Bone regeneration	(J. K. Park et al., 2009)
Titanium surface	Improvement of endothelial cell functions	Cell regeneration	(Donos, Retzepi, Wall, Hamlet, & Ivanovski, 2011)
Nanofibrous matrices	Upregulation of osteogenic genes	Bone regeneration	(Bhattacharjee et al., 2016)
Vitoss® Calcium phosphate	Bone substitute	Mimics bone structure allowing cell adhesion and growth	(Damron, 2007)
Ostim® hydroxyapatite	Bone substitute	Mimics bone structure allowing cell adhesion and growth	(Smeets et al., 2008)

Table 6. Nanopaticle-based anti-inflammatory compounds or nanocarriers of anti-inflammatory compounds

Nanomaterial	Age related disease	Model/Ongoing clinical Phase	Reference
Sesamol-loaded solid lipid NPs	**Menopause-related emotiona Cognitive CNS derangements in ovariectomy**	Rat	(Sandhir et al., 2015)
Novel aspirin loaded oil-in-water (O/W) nanoemulsion	**Various diseases associated with inflammation**	Rat	(S. Y. Tang, Sivakumar, Ng, & Shridharan, 2012)
Novel aspirin loaded water-in-oil-in-water (W/O/W) nano multiple emulsion	**Various diseases associated with inflammation**	Rat	(S. Y. Tang et al., 2012)
RGD-MTX-PLGA-Au	**Rheumatoid arthritis**	Mice	(S.-M. Lee et al., 2013)
Niosomes	**Plaque psoriasis**	Phase I/II	(Lakshmi, Devi, Bhaskaran, & Sacchidanand, 2007)
Nano-structure Liposomes	**Rheumatoid arthritis; Ulcerative colitis.**	Phase III	(Caster, Patel, Zhang, & Wang, 2017)

Nanomaterial	Age related disease	Model/Ongoing clinical Phase	Reference
RA PEGylated gold nanoparticles		Phase III	(Libutti et al., 2010)
	Rheumatoid arthritis		
PLGA NPs		Phase I	(Pearson et al., 2019)
	Coeliac diseases		
Gold nanoparticles		Phase I	(Bruunsgaard et al.)
	Type 1 diabetes		
Uncoated nanoparticle ointment, SOR007		Phase I	(Rizzuto et al., 2019)
	Plaque psoriasis		

Figure 1. The cellular and molecular pathways relating to aging and age-dependent diseases. At the molecular level, persistent DNA damage response (DDR) leads to activation of the tumor suppressor p53, which in turn activates p21 to initiate cell cycle arrest and induce the senescent cells and apoptosis. The generation of ROS results in mitochondria dysfunction inducing by excessive mutations of mDNA. The internal and external stress triggers the formation of misfolded proteins, and their accumulation contributes to ER malfunction. Respiration declines as a result of mitochondria dysfunction and Insulin resistance because of ER malfunction lead to metabolism alternation. The disrupted process involves Sirt1, and AMPK inhibition that adversely affecting lipid metabolism. Another pathway mediates SASP production that invokes pro-inflammatory pathways resulting in a severe inflammatory response. Excessive immune system activity and metabolic dysfunction at the tissue level are considered as critical age-related diseases promotors (Nah, Yuan, & Jung). ETC (Electron transport chain); ROS (Reactive oxygen species); UPRer (ER unfolded protein response); UPRmt (mitochondrial unfolded protein response); AP-1 (activator protein-1); SASP (senescence-associated secretory phenotype); NDs (*neurodegenerative* diseases); CVDs (Cardiovascular diseases).

Figure 2 The cytokines and chemokines-mediated inflammatory cascades triggered by upregulation and downregulation of pro-inflammatory cytokines and anti-inflammatory factors in age-related diseases.