Deep Science Publishing
https://doi.org/10.70593/978-93-49910-64-5_9

Chapter 9: Synergistic pharmacological interventions and lifestyle modifications to decelerate aging: Targeting cellular senescence and metabolic pathways for longevity

[1]Sushil Kumar Middha, [2]Shivangi Mathur, [3]Kavita Singh, [4]Avnish Kumar, [5]Sanwar Mal Kantwa, [6,*]Biswaranjan Paital, [7]Usha T

[1]*Department of Biotechnology, Maharani Lakshmi Ammanni College for Women, 18th Cross, Malleswaram, Bangalore 560012, India, Email: drsushilmiddha@gmail.com*
[2]*Maharishi University of Information Technology, Gautam Buddha Nagar-201304, Uttar Pradesh, (India) Email: shivangimathur2609@gmail.com*
[3]*Department of Chemistry, Institute of Home Science, Dr. Bhimrao Ambedkar University, Agra 282004, India, Email: kavita.rama.singh@gmail.com*
[4]*Department of Biotechnology, School of Life Sciences, Dr. Bhimrao Ambedkar University, Agra 282004.*
[5]*Department of Zoology, B. S. Memorial P.G. College, NH 52, Ranoli, Sikar 332403, India, Email: smkantwa@gmail.com*
[6]*Redox Regulatory Laboratory, Department of Zoology, Odisha University of Agriculture and Technology, Bhubaneswar-751003, India.*
[7]*Department of Biochemistry, Maharani Lashmi Ammanni College For Women, Science Post, Bangalore 560012*
** Correspondence: Biswaranjan Paital, brpaital@ouat.ac.in*

Abstract

The aging process, though inevitable, can be slowed by a combination of pharmacological interventions and healthy lifestyle habits. Medicines such as metformin, rapamycin, and senolytics are being explored for their potential to target key biological pathways involved in aging, including cellular senescence, nutrient sensing, and mitochondrial function. Alongside these medical approaches, lifestyle factors such as a balanced diet, regular physical activity, adequate sleep, stress management, and cognitive engagement play a critical role in maintaining cellular health and delaying the onset of age-related decline. Emerging evidence suggests that an integrated approach—combining targeted medications with positive daily habits—offers the

most promising strategy for extending healthspan, preventing chronic diseases, and promoting vitality in older age. On-going research continues to refine these strategies, aiming to personalize anti-aging interventions for maximum benefit.

Keywords: Anti-Aging Medicines, Balanced Diet, Healthy Aging Habits, Longevity, Lifestyle Interventions, Metformin, Rapamycin, Senolytics, Physical Activity, Sleep and Aging, Stress Management,

9.1. Introduction

Ageing is a complex and gradual biological process marked by cellular decline, reduced physiological function, and increased vulnerability to disease. While it is a natural part of life, scientific advances and lifestyle research have shown that the rate of ageing can be slowed through a combination of medications and healthy habits. Modern medicine has introduced compounds such as metformin, rapamycin, senolytics, and NAD+ boosters, which target key molecular pathways involved in ageing, including inflammation, mitochondrial decline, and cellular senescence. These pharmacological approaches hold promise in extending not just lifespan, but also healthspan—the years of life spent in good health.

Alongside medicinal interventions, lifestyle habits such as regular physical activity, a balanced diet, stress management, quality sleep, and mental stimulation play a critical role in preserving cognitive and physical function as we age. These everyday practices can enhance resilience, delay age-related diseases, and improve overall quality of life. In combination, medicines and positive lifestyle habits offer a powerful strategy to promote healthy ageing and delay the onset of degenerative changes associated with growing older.

9.2. Exercise (Brain and Body)

Both brain and body exercise is linked with ageing. As we know that physical exercise and meditation are good for health. Both are helpful for better physical and mental health. During ageing the ability of the body to maintain homeostasis decreases, and regular exercise increases this ability. Ageing is a very complex process which affects each organ and even each cell in a different way. The functions of skeletal muscles decrease. Regular physical exercise significantly prevents these age-associated loses (Roos et al, 1997). Mattson (2005) reported that this kind of exercise show beneficial effects on brain functions. Physical exercise increases the blood supply to different parts of brain so metabolism increases in neurons. Due to increased metabolism, activity of antioxidant increased and oxidative damage repairing enzymes

also increases (Cotman and Berchtold, 2002; Fabel et al., 2003; Radak et al., 2001, 2006). Neutrophius are activated during physical exercise which not only enhance brain function but also increase the survival of cell (Mattson and wan, 2005). Mattson et al. (2004, 2006) and Radak et al. (2007) also reported that regular exercise decrease the ROS concentration in liver. In conclusion we can say that regular exercise keep you fit and delay your ageing.

9.3. General medicines

Scientists have long known that severely restricting the intake of calories by organisms can extend their lifespans. Most people are unable to sustain severe caloric restriction for long periods, however. So, scientists have been trying for years to find drugs that could produce the beneficial biological effects of caloric restriction causing delayed ageing. Anti-ageing medicines have following advantages over other means-

a) Scientific base: These drugs are passed through various clinical trials. Thus diagnostic and treatment practices using antiageing medicines are more reliable than conventional practices.

b) Evidence based: Antiageing medicine is based on an orderly process of acquiring data for making a scientific conclusion upon which antiageing treatment is assigned.

c) Well documented in Scientific literature: Effect of many natural/synthetic molecules as antiageing molecules is well documented in peer reviewed scientific journals in all over the world.

Following are some of the drugs reported as antiageing agents in market or in various clinical trials.

9.3.1. Rapamycin

Harrison et al. (2009) investigated that rapamycin, an immunosuppressant drug slows ageing in old mice. It was considered as a breakthrough drug for boosted the lifespan of old mice, though having safety issues and the implications for human longevity. Rapamycin inhibits TOR pathway which is an evolutionarily phase preserved consensus nutrient-responsive path providing cellular energy and a monitor of metabolism and development. In humans, there is only one TOR-kinase, known as mTOR or mechanistic TOR (Yip, 2010), instead of TOR1 and TOR2, the two TOR kinase homologues found in yeast (Loewith, 2011) and well known targets of Rapamycin.

However, despite the lack of explicated mechanism, rapamycin and its analogs or ‘rapalogs’ have long been considered a probable molecules for the pharmacological intrusion of ageing. Though, research into the relationship between TOR inhibition, rapamycin and ageing is still ongoing. Johnson et al. (2013) have reported that rapamycin has shown promising results in cancer disease. FDA has already approved

rapamycin for renal cell carcinoma, mantle cell lymphoma, and pancreatic cancer. The mechanism behind is an up regulation of mTOR signaling pathway in cancer patients by mTOR inhibition. Though there is a major drawback about drug being cytostatic rather than cytotoxic and rooting tumour growth to slow or stop but not reducing tumour size (Xie et al., 2016).

9.3.2. Torin

Another such exemplary drug was identified and developed by AstraZeneca as Torin1 and Torin2, a potent ATP-analog mTOR inhibitor (Xie et al., 2016). Both of the drugs were intensely worked through and can inhibit both mTORC1 and mTORC2 (Johnson et al., 2013). Torin1 was found to be more effective than rapamycin in inhibiting senescent and ageing morphology in human cells (Johnson et al., 2013). Torin1-fed fruit flies demonstrated improved lifespan without easing down fertility (Mason et al., 2018).

9.3.3. Resveratrol

Resveratrol is one of the most widely studied molecules in bio-gerontology (Bhullar, 2015) due its notable ability to counteract different age-related diseases in mammals with an apparent lack of toxicity (Baur, 2006). It was first described in ethanol extracts of the white hellebore Veratrum grandiflorum in 1939 and was characterized as a phytoalexin (Bhullar, 2015). In recent years, it has been shown to be present in grapes, red wine and a few other species under stress conditions (Wang et al.. 2010). Mattivi and Korhammer (1995) explained the two isomeric configurations of this compound (3, 5, 4'-trihydroxystilbene) named trans-(E) and cis-(Z), which undergoes isomerization on exposure to ultraviolet radiation (Mattivi et al., 1995).

The antioxidant pharmacore activity, which scavenges free radicals, in resveratrol can be, traced to the 4-hydroxystilbene skeleton (Cao et al., 2003, Queiroz et al., 2009). Several studies showed that it inhibits both the formation of copper-catalyzed LDL oxidation (Frankel, 1993), and the peroxidation of membrane lipids (Tadolini, 2000). It also has the ability to restrict the release of inflammatory mediators that contribute to cardiovascular diseases (Rotondo et al., 1998), prevent the formation and growth of different types of cancer even by topical application (Jang et al., 1997) and is neuroprotective (Virgili et al., 2000). There are a few studies that also report negative effects such as DNA damage (Breinholt, 2003) and increased atherosclerosis (Wilson et al., 1996).

Inhibition of cyclooxygenases enzymes COX-1 and COX-2 (Murias, 2003), various cytochrome P450s (Yu et al., 2003), NADPH oxidase (ROS production enzyme) (Gliemann et al. 2016), PKD (protein kinase D) (Haworth 2001), S6 kinase

(Armour et al., 2009), the transcription factor AP-1 (activator protein 1), and activation of sirtuins is considered to bet the main mediators for the health enhancing benefits of resveratrol. Sirtuins Metabolic diseases and mitochondrial environment is influenced by these regulators (Lagouge et al., 2006), and are actively involved in inflammation, carcinogenesis, lipolysis and other pathologies (Ono et al., 2008, Kundu and Surh, 2006; Borradaile, 2009). Several in vitro and in vivo eukaryotic models have shown resveratrol'a ability to increase lifespan (Wang, 2012) such as budding yeast, in worms (Tissenbaum, 2001), fruit flies (Rogina, 2004), short-lived fishes (Valenzano et al., 2006, Yu, 2012, Liu et al., 2018), obese mice (Baur, 2006), and rhesus monkeys fed a high-fat/high-sucrose diet (Jimenez-Gomez, 2013).

Burnett et al. (2011) have reported that there have been doubts on the robustness of the effects of sirtunis on lifespan control due to relevant experiments in worms and Drosophila (Burnett, 2011). Of the seven sirtuins, mammalian SIRT1 is the most characterized and it regulates various cellular processes through the correct activation of AMPK and inhibition of mTOR signaling.

Resveratrol targets SIRT1 in vivo by enhancing deacetylation of non-tagged peptide substrates through a direct allosteric binding (Howitz et al., 2003, Price et al., 2012, Hubbard et al., 2013; Lakshminarasimhan, 2013). Its overexpression is beneficial in cellular models of Alzheimer's disease (Kim et al., 2007), cancer (Liu et al., 2009), type II diabetes (Milne et al., 2007), and cardiovascular disease (Borradaile, 2009). Since there are no large-scale studies on lifespan of healthy humans to date and even with all the existing positive data, healthy wild-type mice show no increase in longevity by resveratrol treatment (Li and Lin, 2018) the effects of resveratrol on mammalian lifespan in population studies is limited. However it shows a remarkable capacity to enhance health and longevity in the presence of pathologies due to its pleiotropic effects (Howitz, 2008). Nonetheless, it remains inconclusive whether resveratrol contains life-prolonging properties (Pallauf et al., 2016).

9.3.4. Metformin

Metformin is the most widely used oral hypoglycaemic agent and a first-line treatment for non-insulin-dependent (type 2) diabetes (Custodero, 2018). This compound is derived from a natural product called galegine obtained from the plant French lilac *Galega officinalis* (Rena, 2017). Herbal medicine employed the use of extracts of this plant in medieval times for the treatment of painful/frequent urination accompanying diabetes mellitus. The glucose-lowering activity of galegine was discovered in 1920s at the time, it was proved to be toxic in humans, but after re-introduction to clinical use in 1957 after it was established as a safe and effective therapy for the treatment of type 2 diabetes (Bailey, 2004).

The primary molecular mechanism of this dimethylbiguanide has remained unclear even after its wide clinical usage for over 60 years mostly because it was not designed to target a specific pathway or disease and (Custodero, 2018). The suppression of >60% gluconeogenesis/lipogenesis in the liver and the increase in insulin-mediated uptake of glucose in muscles attributed to different pathways including AMPK have been established by many studies (Hundal et al., 2000,Takashima et al., 2010). The adenosine monophosphate-activated protein kinase (AMPK) pathway is an evolutionarily conserved signaling pathway that senses cellular energy status through AMP/ATP and ADP/ATP ratios promoting catabolism and inhibiting anabolism (Garcia and Shaw, 2017).

AMP-activated protein serine/threonine kinases are heretotrimeric consisting of one enzymatic and two regulatory subunits. Upstream kinases and phosphatases tightly regulated AMPK. AMPK is directly linked to ageing as coordinates and controls repair and housekeeping mechanisms linked with maintenance, senescence and lifespan, such as auto-phagocytosis (Mihaylova and Shaw, 2011), ER stress suppression (Dong et al., 2010), oxidative stress alleviation (Li et al. 2009) or suppression of inflammation (Salminen et al., 2011). Overexpression of AMPK can extend lifespan in worms (Curtis et al., 2011) and Drosophila (Funakoshi et al., 2011). Gene deletions in mammals have severe detrimental effects hence making it very complicated (Viollet et al., 2003). AMPK activation pathological conditions such as stroke can induce additional cellular and tissue damage (Dyck and Lopaschuk, 2006, McCullough et al., 2005).

It was observed that AMPK activity increases within muscles of young but not old rats suggesting that the activation ability on certain stimuli decreases during lifespan (Reznick et al., 2007). Age-related diseases such as cardiovascular diseases and metabolic syndrome are being linked with decline in the AMPK activation ability with ageing (Turdi et al., 2010,). Metformin and aspirin have shown potent activation of the pathway. Metformin-mediated actions involve phosphorylation/activation of AMPK in its catalytic α1/α2 subunits at threorine-172, mediated by LKB1 (liver kinase B1) (Zhou, 2001). This triggers the inhibition of the mitochondrial respiratory chain complex I, which produces a decrease in ATP levels together with an increase in the ratios of ADP/ATP (Owen and Halestrap, 2000) and AMP/ATP that activate AMPK (Xiao et al., 2011,). It leads to phosphorylation of CRTC2 (CREB-regulated transcription coactivator 2) and CBP (CREB-binding protein), downregulating gluconeogenic gene expression (Koo et al., 2005, He et al., 2009).

Another study based on results from AMPK α1/α2 knockout mice, indicated that the decrease in glucose production occurs through the regulation of gluconeogenesis flux in response to a decrease of the hepatic energy availability (Foretz et al., 2010). Metformin is being explored for lifespan extension as they have been attributed to transcription, genome stability, epigenome marking, metal-interactive regulation of protein function that inhibit pro-inflammatory proteases and anti-apoptotic pathways independent of its glucose reducing effects (Foretz et al., 2010, Cuyàs et al., 2018, Finley, 2018). *S. cerevisiae* is one of the organisms reporting the same where extension of chronological lifespan was reported due to glycation inhibition (Kaeberlein and Guarente, 1999). *C. elegans* showed impairment of folate and methionine metabolism in the intestinal microbiome on metformin treatment (Cabreiro, 2013), while reduced adipose tissue inflammation was observed in mice (Shin, 2014). Within fly intestinal stem cells, metformin inhibits ageing phenotypes in an Atg6 (autophagy-related 6)-dependent manner (Yuan et al., 2018).

The significant difference observed between resveratrol and metformin is that clinical trials in humans confirmed the significant reduction of CRP (C-reactive protein) levels, (marker of systemic inflammation) due to metformin, this is not observed with resveratrol treatment (Custodero et al., 2018). Cellular stress-induced AMPK activation promotes the activity of the splicing factor-associated protein p32 which acts as endogenous inhibitor of SRSF1 and binds to mitochondrial mRNAs in vivo, regulating their efficient translation. p32 is pivotal in coding for proteins involved in oxidative phosphorylation. p32 also affects the transcriptional activity of NFE2L2 (Nuclear factor erythroid-derived 2-like 2), which is a main regulator of the antioxidant response disrupted in progeria cells (Finley, 2018). The health span-extension effects of metformin can also be explained through the inhibition of nutrient/energy-sensing metabolic pathways such as the insulin/IGF-1 (insulin-like growth factor 1) and mTOR (Tanokashira, 2018). The overall favourable effects of metformin in physiological functions through multiple modest, but substantial, effects, combined with its well-characterized profile, suggest that it may be beneficial for the treatment of normal or pathological ageing (Finley, 2018).

9.3.5. Aspirin

Acetylsalicylic acid is the most common nonsteroidal anti-inflammatory drug and globally used medication. It is widely used for the treatment of pain, fever, inflammation, platelet aggregation, prevention of cardiovascular pathologies and cancer (Thun and Patrono, 2012). Its active component salicylate is chemically synthesized from the bark of the willow tree Salix alba. Aspirin suppresses prostanoid biosynthesis through the irreversible inactivation of COX-1 (prostaglandin-endoperoxide synthase, PTGS1) and the inhibition of COX-2 (PTGS2) (Vane, 1971).

The latter has multiple effects such as uncoupling oxidative respiration through proton transport on the inner mitochondrial membrane (Petrescu,1997); acetylation and inhibition of G6PD (glucose-6-phosphate dehydrogenase), which catalyzes the first reaction in the pentose phosphate pathway involved in the regulation of oxidative stress (Ai et al., 2016,); activation of AMPK via Thr-172 phosphorylation; and activation of protein kinase IKKβ (inhibitor of nuclear factor kappa-B) that arrests the pro-inflammatory transcription factor NF-κB (Yuan et al. 2001). Salicylate is known to competitively inhibit the binding of acetyl coenzyme A (the sole acetyl group donor) to acetyltransferases such as EP300 (E1A-associated protein p300) resulting in inhibition of its activity and inducing the autophagic cascade that enhances longevity, still observed in the absence of AMPK (Madeo et al., 2014, Pietrocola et al., 2018).

Aspirin increases the maximum and mean lifespan of different organisms through pleiotropic molecular mechanisms and delays the onset of various age-related diseases (Huang et al., 2017).Attenuation of endogenous levels of ROS as well as upregulation of antioxidant genes together with activation of the transcription factors DAF-12 and DAF-16 that increase lipid hydrolysis and inhibit the proliferation of germline stem cells have shown to increase lifespan in worms (Ayyadevara et al., 2013). Fruit flies showed a decrease in female fecundity resulted by the inhibition of the heme peroxidase Pxt (COX-like) facilitator of follicle maturation (Tootle, 2008). These effects are accompanied by increased resistance to stress and improved locomotor activity that are overall mediated by the Pkh2-ypk1-lem3-tat2 signaling pathway (Danilov et al., 2015,). In mice, aspirin increases the survival of males but not females (Strong, 2008). Different trials have shown low risk of cancer incidence and mortality, protective effects against Alzheimer's and Parkinson's disease (Bardia et al., 2007, Mills et al., 2012). Tests to determine the increase healthspan and lifespan of humans are yet to be done (Madreiter et al., 2018).

9.3.6. Mirtazapine

Rangaraju et al. (2015) studied effect of mirtazapine in Caenorhabditis elegans. They reported that atypical antidepressants activate a neuronal mechanism that regulates the response to oxidative stress throughout the animal. While the activation of the oxidative stress response by atypical antidepressants depends on synaptic transmission, the activation by reactive oxygen species does not. Lifespan extension by atypical antidepressants depends on the neuronal oxidative stress response activation mechanism. These effects on oxidative defense systems may be more than just an indirect correlation, as suggested by experiments showing that certain antioxidants have antidepressant-like effects in rodents as well as in humans (Ferreira et al., 2008). Other studies also confirmed effect of mirtazapine as anti-oxidative drug demonstrating that Mirtazapine treatment protects kidneys from oxidative damage caused by

ischemia–reperfusion injury and neurons from oxidative damage caused by cisplatin, in rats (Tok et al., 2012; Gulec et al., 2013).

9.3.7. Antihistamine cyproheptadine

Antioxidant pills Reactive oxygen species are closely related to ageing, enzymes remove reactive oxygen species, superoxide dismutase (SOD) and catalase expression to and extend the life of C. elegans and Drosophila (Sampayo et al., 2003). 5 life-lengthening effects were observed in the drugs that eliminate reactive oxygen species EUK-8 and EUK-134). 50 mixed with medium M EUK-134, administered to adult nematodes increased life expectancy is 54%. EUK-8 and EUK-134 did not affect fertility and body size (Keaney et al., 2004; Kim et al., 2008).

9.3.8. Lithium

Research has shown Lithium treatment on worms increased both lifespan and healthspan and improved mitochondrial energy output (Zhi et al., 2004). Lithium might improve mitochondrial function by increasing the turnover of dysfunctional mitochondria (Zhi et al., 2004).However, another study of flies found the opposite outcome: lithium exposure did not extend lifespan and actually reduced the female fly's lifespan advantage (Fengge et al., 2005). A correlation was found when researchers measured the longevity of people and lithium in their water. There was a decreased risk for all causes of death in Japanese neighborhoods with higher lithium levels. The study concluded that "long-term low-dose exposure to lithium may exert anti-ageing capabilities and unambiguously decreases mortality in evolutionary distinct species" due to increase NAD+, which is associated with longevity (Kim et al., 2011).

9.3.9. Challenges and pitfalls

Various pathways and genes are known to control ageing in model organisms (Bonkowski, 2016), encourageing a new generation of anti-ageing drugs and companies. Efforts range from drug discovery to big-data methods and direct-to-consumer (DTC) strategies (Jayachandran et al., 2021). Challenges and pitfalls of commercialization include dependence on findings from short lifespan model organisms, poor biological understanding of ageing, and hurdles in conducting clinical trials for ageing. A large number of potential ageing-associated molecules and targets exist, but due to long validation times only a small proportion can be experimented for clinical applications.

9.4. Nano-medicines

Nanotechnology is a revolutionary way of understanding technology and the process of manufacturing it in different sectors of industries such as transportation, nuclear weapons, detection systems, and telecommunications to name few sectors

which nanotechnology will have a major impact. Specifically, nano-medicine, which is the application of nanotechnologies to medicine, is considered the field where nanotechnologies may noticeably improve medical practice for prevention and therapeutic purposes. The vastness of nanotechnology applications leaves many unanswered questions on the hazards related to human health from exposure of nanoparticles on the human body. Applications of nanotechnology for treatment, diagnosis, monitoring, and control of biological systems has recently been referred to as "nanomedicine" by the National Institutes of Health. Research into the rational delivery and targeting of pharmaceutical, therapeutic, and diagnostic agents is at the forefront of projects in nanomedicine. These involve the identification of precise targets (cells and receptors) related to specific clinical conditions and choice of the appropriate nano-carriers to achieve the required responses while minimizing the side effects.

Mononuclear phagocytes, dendritic cells, endothelial cells, and cancers (tumor cells, as well as tumor neo-vasculature) are key targets. Today, nanotechnology and nano-science approaches to particle design and formulation are beginning to expand the market for many drugs and are forming the basis for a highly profitable niche within the industry, but some predicted benefits are hyped. This article will highlight rational approaches in design and surface engineering of nano-scale vehicles and entities for site-specific drug delivery and medical imaging after parenteral administration. Potential pitfalls or side effects associated with nanoparticles are also discussed.

The novelty of nanotechnologies demands a new approach in order to fully understand its broad applications, evaluate potential benefits, and assess potential risks on human health. However, because nano-medicine is a nascent science its risks and benefits are only hypothetically assessed at this stage. The lack of consolidated knowledge and the extensive medical literature of experimental data do not allow a clear assessment of the risks-benefits associated to this new technology. This lack of knowledge that currently surrounds the area of nano-medicine makes it difficult to anticipate adequate regulatory responses in nano-medicine and raises several regulatory questions.

Understanding how technology operates and how it is constructed may now be approached in a new light thanks to nanotechnology. It will have a significant influence on a great number of different businesses, some of which include transportation, nuclear weapons, detecting systems, and telecommunications, to mention a few. It is believed that nanomedicine, which refers to the use of nanotechnologies in the medical field, will be the area in which nanotechnologies will be able to make the greatest

impact on both the prevention and treatment of diseases. Because nanotechnology may be applied in so many different contexts, there are still a lot of unanswered issues regarding the potential negative effects that being exposed to nanoparticles on the human body could have on our health. Recently, the National Institutes of Health came up with the phrase "nanomedicine" to characterize the use of nanotechnology to treat, diagnose, monitor, and regulate biological systems. This term was derived from the word "nanotechnology." In the field of nanomedicine, the most significant research initiatives are those that investigate clever ways to administer and target pharmaceuticals, therapeutics, and diagnostic agents.

These include locating the precise targets (cells and receptors) for a particular clinical condition and selecting the appropriate nanocarriers in order to achieve the desired results while experiencing the least amount of adverse effects possible. The mononuclear phagocytes, dendritic cells, endothelial cells, and malignancies themselves are the primary targets (both the tumour cells and the new blood vessels that grow into them). Nanotechnology and nanoscience techniques to creating and producing particles are beginning to develop the market for numerous pharmaceuticals and establish a very valuable niche in the business, despite the fact that some of the anticipated advantages have been overblown. After parenteral administration, the topic of discussion in this paper will be logical methods to the design and surface engineering of nanoscale vehicles and entities for site-specific drug delivery and medical imaging. There is also discussion over the potential drawbacks or adverse effects of nanoparticles.

Due to the novelty of nanotechnologies, it is necessary to adopt a novel style of thinking in order to completely comprehend the extensive number of applications for these technologies, as well as to assess the potential advantages of using them and the potential dangers they pose to human health. However, due to the fact that nanomedicine is still in its infancy as a subject of research, the dangers and advantages associated with it can currently only be hypothesized. Because we do not have enough information on this new technology and the medical literature has a lot of data gleaned from experiments, it is difficult to determine both the risks and the advantages of using it. It is difficult to forecast the appropriate actions that regulators will take regarding nanomedicine at this time since we do not yet have adequate information. This gives rise to a variety of concerns about regulatory compliance.

9.4.1. Nanomedicines against immune and inflammatory disorders

Inflammation is a defensive response involving immune cells, the immune system as a whole, blood vessels, and chemical mediators. Inappropriate

immunological or inflammatory responses, as well as cells' failure to respond effectively to naturally occurring immune or inflammatory processes, are at the foundation of a wide range of illnesses and ailments. Complement dysfunction or over activation has been linked to autoimmune illnesses, inflammatory diseases, neurological diseases, ischemia-reperfusion damage, and cancer. For example, activation of the complement cascade's alternate pathway contributes to the creation of the powerful anaphylatoxins C3a and C5a, which also play roles in a number of inflammatory diseases. Diseases mediated by the complement system include multiple sclerosis, rheumatoid arthritis, and age-related macular degeneration (AMD). PNH (paroxysmal nocturnal hemoglobinuria) is one more disorders. The age related illnesses can be reduce by targeting Factor D which is an appealing target for complement cascade suppression or modulation due to its early and critical participation in the alternative complement pathway, as well as its possible role in signal amplification within the classical and lectin complement pathways. The inhibition of factor D (the pathway is effectively stopped) could reduce the formation of the membrane attack complex. Factor D inhibitors can take the form of prolyl molecules.

In one embodiment, "providing a compound with at least one additional active agent" might imply that the compound and the extra active agent(s) are delivered concurrently suitable administrable dose. Various healthcare providers (Biocryst Pharmaceuticals, USA; Novartis USA; Bristol-Myers Squibb; Japan Tobacco Inc; Ferring B.V. and Yamanouchi Pharmaceutical Co. lTD; Alexion Pharmaceuticals etc.) have patented their medicinal formula containing the chemical and/or the additional active agent. These compounds are oral tablets, oral capsules, oral liquids, inhalation, injection, suppositories, parenteral, sublingual, buccal, intravenous, intraaortal, transdermal, polymeric controlled delivery, non-polymeric controlled delivery, nano or microparticles, liposomes etc. that is given through appropriate routes.

Microparticles and/or nanoparticles may be utilised in the following forms: aerosol, cream, gel, gel cap, pill, injection or infusion solution, capsule, tablet, syrup, transdermal patch, subcutaneous patch, dry powder, inhalation formulation, in a medical device, suppository, buccal, or sublingual formulation, parenteral formulation, ophthalmic solution or suspension, or ophthalmic solution or suspension. All of these substances have useful applications in the pharmaceutical industry and may be consumed without risk.

9.4.2. Nanomedicines for cell senescence

Nanomedicines' physicochemical and pharmacological properties may be changed to increase their effectiveness against neurological diseases. This would significantly improve the therapeutic process due to targeted action on weak cells. It may easily work in harmony with blood brain barrier. Despite numerous positive outcomes, there is still a lot of anxiety over the research and clinical application of nanomedicines. The complexity of the nanomedicine formulation that has to be made commercially available for human usage might be lessened by the researchers. Due to the small number of studies that have been done so far, its safety, toxicity, and therapeutic effectiveness at a lower dose must also be taken into consideration. For the transition of nanomedicines from pre-clinical to clinical trials against neurodegenerative illnesses targeting inflammasome cascade, further research is necessary (Chaturvedi et al., 2022).

9.4.3. Nanoparticle based dermal anti-aging process

The cosmeceutical industry views nanoparticles as a potent tool for enhancing the efficacy of currently available drugs. Numerous studies on organic and inorganic nanoparticles for antiaging purposes have been conducted. The process of ageing is a constant deterioration in physiological parameters' functional capacity. One of the most sensitive organs, the skin, exhibits early ageing symptoms that are mostly influenced by external as well as intrinsic factors. The physiological aberrations associated with skin ageing are controlled by various complex interactions at the cellular and subcellular levels, which result in the visible morphological and anatomical alterations associated with skin ageing.

The cosmeceutical industry views nanoparticles as a potent tool used for both enhancing the efficacy of currently available drugs and as a cutting-edge independent therapy. The nanoparticles are also becoming potential choice for skin defense against external factors like UV radiation and pollution (Paital and Agrawal, 2020). The intrinsic factors based influence on cellular, subcellular, and epigenetic components are also under studies to stop skin aging processes. Modern formulations are importantly includes organic and inorganic nanoparticles based on plants for anti-aging use. These studies are exploring the mechanism behind their mode of action to prevent skin ageing. Some studies showing that targeted specific cellular and molecular pathways using nanoparticles helps to increase the action of anti-aging drugs **(**Bhatia et al., 2022).

9.4.4. Effects of nanoparticles, a new horizon

Nanoparticles (NPs) are materials of the diameter that fit within a few hundred nanometers. This size provides them with bodily and chemical residences in order to

make them highly bioavailable (ISO /TR 27628, 2007, Ostiguy *et al.*, 2006, Handy *et al.*, 2008). NPs find huge potential in medical applications and produced by means of chemical processes which are further used in different fields like fertilizers, biomedicine, electrical appliances, pharmacology and cosmetics (Matranga and Corsi 2012). Research done on thisrevealed that Ag-NPs, TiO2-NPs, and ZnO-NPs turn to be toxic for marine species (Gottschalk *et al.*, 2009). NPs are discovered in water and land ecosystems, where they are consumed by biotic creatures wherein they acquire, before removal by means of the defense machine or other metabolic pathways. In organisms, NPs comprise molecules with unique chemistry; intrude with the ordinary physiological machineries of the fetus, young animals, and grown-ups. These mechanisms involve in their ageing and senescence of cells through tissue remodeling and mesenchymal transition (Exbrayat *et al.*, 2015).

9.4.5. The mechanism of aging under nanoparticle exposure

Ageing affects almost all the tissues on continuous exposure to nanoparticles as they are busy generating ROS mediated tissue destruction. They are classified into chronological and photo-ageing which affects the dermal and epidermal tissue layers largely. The cellular and metabolic abnormalities could be noted in these cells such as production of excessive elastin, thickening of collagen fibres and keratinocyte irregularity. They could be monitored clinically through external physiological changes also (Mukherjee *et al.*, 2006). Oxidative damage is prompted by internal or external reactive oxygen species (ROS) that can motive harm to a chain of cellular additives, for biomolecules like DNA/RNA, cellular proteins, phospholipids and so on. Mitochondrial breathing converts oxygen into a series of reactive components, mainly O_2 and (OH) loose radicals, and results in oxidative related random deletions that harm and spread to tissues (Muller *et al.*, 2007, Wenshu *et al.*, 2015).

9.4.6. Effects of NPs on Terrestrial Animals Species

Today, numerous residing models are used a good way to understand the influences of NPs on animals. Research involving mammals, which include mice, or small fishes, along with the zebra fish, proved that nanoparticles produced deadly results at the developmental stages of embryos (Blum *et al.*, 2012, Sun *et al.*, 2013). Some experiments involving *in vitro* and *in vivo* cultures of animal tissues exhibited that silver nanomaterials brought about an oxidative pressure featured by properly reactive moieties possessing unfastened oxygen radicals (ROS), geno toxicity with DNA smash, or apoptosis leading to senescence and death (Kim *et al.*, 2013). Studies concerning the ecological impact of fabricated nanoparticles are hindered by way of the lack of queries to locate and estimate them in water, land, and animals. Neutron

activated experiments has been extensively performed to look at the results of Cobalt nanomaterials in the earthworm *Eisenia fetida* (Oughton *et al.*, 2008). Few experiments completed with mice showed actual lethal consequences of NPs on cognitive and behavioral disorders. In the rats, short exposures to Cu-NPs (forty and 60 nm diameter) triggered the multiplication of endothelium of brain vessels once they had been introduced to lower concentrations (approximately 1.5 μg/mL). Higher concentrations (50 μg/mL) brought on a boom of prostaglandin (Trickler *et al.*, 2012).

Ag-NPs kindled the thinning effect of the body in rats, with a decrease in its propulsive pastime. The damage of glial cells and reduction of myelin fibre in tissues tend to activate heat shock proteins due to the accumulation of ultrafine nanoparticles in blood brain fluxes promoting neuronal accidents (Trickler *et al.*, 2010). Another study conducted on rat models revealed a short term treatment to Ag-NPs stimulated the blood-brain barrier, promoting a pro inflammatory response that may broaden a brain infection followed with neurotoxic results. Cytotoxic outcomes were induced via the smallest NPs in comparison to largest ones (Exbrayat *et al.*, 2015).

9.4.7. Influence of metallic nanoparticles in ageing

Metallic nanoparticles are widely being used in food industries, medicine and pharmaceutics. Silver nanoparticles are largely active and can penetrate blood brain barrier which accumulates there in high amounts. These particles are involved in influencing the cognitive and behavioral properties of animals. *Ex vivo* experiments have demonstrated the appearance of ROS in cells and found to influence calcium signals in experimentations (Antsiferova *et al.*, 2018, Kim *et al.*, 2014). Nanoparticles including silver and oxides of zinc and copper are regularly used as microbicidal agents. Still, after the release of pollutants into the ecosystem, harmful results also can have an effect on non-target organisms (Sharma *et al.*, 2009). The effects of copper and silver nanoparticlesin the size range of 50 to 60 nm have been more essential than aluminum nanoparticles with sizes of 50 to 60 nm. It became additionally found that the consequences have been more crucial in rats than those of mice (Zhiquan *et al.*, 2018).

9.4.8. Influence of nanoplastics in ageing

Occurrence of nanoplastics in water bodies is a prevalent concern besides their toxicity and other hazardous effects. Prolonged exposure to polystyrene like nanoplastics are posing age related problems and paves a dangerous way for their senescence and cell death, as per the studies done in small animals. One of the major model species is water flea, *Daphnia pulex* which has expressed stress genes and

provoked physiological changes. These changes recorded could be attributed to all other aquatic animals exposed to such nanoplastics. Polystyrene nanoplastics and their dispersants have reported to stimulate the production of ROS and developmental defects in the larvae of sea urchins. They can cross blood brain barriers and hence affect the metabolism and behavior of fishes like *Carassius carassius* which are further associated with the senescence and ageing of cells (Koelmans *et al.,* 2015, Spannbrucker, 2019).

9.4.9. Influence of carbon nanoparticles in ageing

Senescence of lung epithelial cells has been observed on inhalation of combustion derived carbon nanoparticles (Bartling and Hofmann 2018; Jena et al. 2022). Diseases related to ageing and senescence such as the chronic pulmonary disease and pulmonary fibrosis also has been reported. Repetitive exposure to carbon nanoparticles have shown to produce senescent like phenotype which results in the loss of function of communication in gap junctions. Prolonged doses of carbon nanoparticles stimulated ageing in cells and provoked age related diseases (Wenshu *et al.,* 2015).

9.4.10. Application studies of Fullerene in ageing of animals

Fullerenes and their derivatives have fascinated sizeable interest in biomedicine. Polyhydroxyl fullerene (fullerenol), a soluble fullerene derivative, is confirmed as an appealing antioxidant. To similarly determine their anti-aging and anti-stress ability, *Caenorhabditis elegans* (*C. elegans*) has been utilized as a small animal model to assess the impact of fullerenol on the growth, conduct and anti-stress ability features *in vivo*. The records display that fullerenol has very little manifestly toxicity on nematodes and can postpone *C. elegans* ageing underneath regular circumstance. Further research displays that fullerenols attenuate endogenous ranges of ROS generation and presents defense to *C. elegans* under pressurized conditions by up-regulation of genes for stress regulation and improves lifespan (Jun *et al.,* 2010). Functionalized fullerenes stimulate key organic responses, along with cell viability, intracellular ROS, cellular proliferation and cellular cycle reactions. These molecular mechanisms have been attributed to the variations in expressing the HERC5 genes of the Ubiquitin family (Svetlana *et al.,* 2020).

9.4.11. Nano ageing, an emerging Science

Impact of nanoparticles on cellular and physiological senescence is largely an unexplored research area (Chen-Chen and Xiaoxiao 2021). To date, few works concerning the outcomes of NPs on species residing in soil like small mammals or worms, semi aquatic animals, which include amphibians, freshwater or marine species,

together with Pisces, invertebrates, phyto and zooplankton have been performed. Research on the influence of nanoparticles on aging is divided into 2 predominant streams: one being the exploration of numerous pathophysiological and molecular activities accountable for growing older and the other being research on various anti-growing old dealers. Although an awful lot tricky mechanistic studies were performed for know-how the pathophysiology of growing older, they will nevertheless preserve until the entire cascade of molecular activities answerable for intrinsic/photo aging is elucidated. Under normal lifestyle conditions, nanoparticles induce a delayed ageing in worms. Meanwhile, underneath oxidative pressure, nanoparticles show obvious anti-stress impact with the help of its ROS engulfing property at cellular levels and by the up regulation of numerous stress reducing genes (Hui *et al.*, 2022). Nanoparticles are found to behave indifferently both up-regulating and down-regulating the ageing phenomena based on their particle size, surface characteristics and dosage.

Conclusion

Slowing the ageing process is no longer just a theoretical idea—it is becoming a practical goal through the combined power of scientific innovation and healthy living. While emerging medicines such as metformin, rapamycin, and NAD+ boosters show promise in targeting biological pathways linked to ageing, they are most effective when supported by consistent, healthy lifestyle habits. Simple yet powerful practices—like regular exercise, balanced nutrition, adequate sleep, stress management, and mental engagement—can significantly delay the onset of age-related decline and promote long-term well-being. Together, these interventions help to extend not only lifespan but also healthspan, allowing individuals to enjoy a higher quality of life as they age. In conclusion, a proactive approach that integrates both medical advances and daily healthy habits offers the most effective path to ageing gracefully, maintaining vitality, and preventing age-associated diseases.

Author Contributions: "Conceptualization, methodology, software, validation, formal analysis, investigation, resources, writing—original draft preparation, and editing: SKM and BRP. Writing—original draft preparation, and editing, data curation and validation: SM, KS, AK, SMK and UT. The authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by DBT Star College Scheme, 12th batch, Granted to College of Basic Science and Humanities under the cordinatorship of Dr Biswaranjan Paital (HRD-11011/33/2022-HRD-DBT)", SKM also acknowledges the facilities provided by DST-FIST for PG Level O facility (SR/FST/College-2018-404) and DBT-BIF facility at Maharani Lakshmi Ammanni College For Women (mLAC). SKM also obliged to ANRF- Teachers

Associateship For Research Excellence (TARE) fellowship (TAR/2022/000392) by Department of Science and Technology, GoI and “The APC was not funded by anyone”.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: All data are published in this article. The authros declare that this manuscript is an original work, prepared with the consent and contribution of all listed authors. It has not been submitted to, nor published in, any other journal or platform. All figures and tables are drawn using appropriate Creative Commons platforms with proper attribution. We as authors declare that there are no conflicts of interest related to this work.

Acknowledgments: Encouragement by the mentor of BRP Prof. GBN Chainy, former Head, Department of Zoology and Department of Biotechnology, Utkal University, Bhubaneswar, India is duly acknowledged. SM acknowledges and expresses gratitute to the Management, administration and Academic officials of MUIT, Noida Campus for their valuable support during preperation, and submission of the manuscript.

Conflicts of Interest: “The authors declare no conflict of interest.” “The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results”.

Citation: Middha SK, Mathur S, Singh K, Kumar A, Kantwa SM, Paital B, Usha T (2025) Synergistic pharmacological interventions and lifestyle modifications to decelerate aging: Targeting cellular senescence and metabolic pathways for longevity. *In*: Paital B (ed) *Defy the Clock with Slow Aging*, 1st edn. Deep Science Publishing, USA, pp. 93-110, https://doi.org/10.70593/978-93-49910-64-5_9