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REVIEW ARTICLE

# The Triple-Antioxidant Alliance: A Review of Lycopene, Resveratrol, and Vitamin E in Synergistic Anti-Aging Strategies

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## Abstract

Progressive decline in health as people age is caused by several biologically related mechanisms known as hallmarks of aging. These mechanisms include chronic inflammation, oxidative stress, and cellular senescence. Monotherapy using these hallmarks alone has not worked much in clinical application. Therefore, there is a movement toward developing synergistic solutions to target the hallmarks of aging with multiple nutraceutical agents. In this review article, we will discuss the scientific rationale and new evidence supporting the use of three nutraceutical agents – lycopene, resveratrol, and Vitamin E – taken together in order to utilize their synergistic properties in an anti-aging regimen. Second, the authors believe that using these three nutraceuticals together in one formulation exceeds what each would do alone due to their complementary and synergistic mechanisms of action. For example, lycopene and Vitamin E utilize lipid-based antioxidant mechanisms, whereas resveratrol produces signaling through hormesis, which upregulates endogenous repair processes and autophagy. Thus, these three nutraceuticals can combat many hallmark mechanisms of aging, including but not limited to genomic instability, dysregulation of nutrient sensing, and alteration of intercellular communication. In addition, we evaluate the effect of the synergistic action of these nutraceuticals upon biomarkers in humans and discuss how they have similar or complementary pharmacodynamics and pharmacokinetics. Finally, we also discuss the challenges of evaluating long-term outcomes of these agents in humans because of inter-individual variability and their negative effects, such as bleeding from anticoagulant therapy. This initial-stage drug combination was developed to treat aging with the expectation that it will pave the way for future personalized and holistic approaches to extending our health as we live longer lives.

**Key words:** Antioxidant, lycopene, nutraceuticals, resveratrol, synergistic

## INTRODUCTION

Aging is biological and will occur to every living thing eventually; however, the way that it is experienced will be different for many people. Aging is defined as declining physiological systems leading to more susceptibility to death and less ability to live (supporting). The effects of aging are easy to see, but the causes behind why we age are not very easy to understand. The main mechanisms behind how aging occurs are telomere shortening, genomic instability, epigenetics, and poor proteins/building blocks of cells.[1] Traditional approaches to promoting healthy aging include changing one's way of living through such means as diet, exercise, and reducing stress. These measures are critical but do not target specific biological mechanisms related to the aging process. Therefore, the need for pharmacological approaches that specifically consider the biology of aging is evident. New compounds, including rapamycin, metformin, and senolytics, are now being tested in clinical trials and represent a significant shift in treating all age-related conditions by treating the underlying cause of aging (age itself) as a singular illness.[2]

Using a combination of different drugs with diverse mechanisms would likely be better than using only one medicine to treat aging. The multidrug therapy strategy for treating aging will take cues from oncology and human

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immunodeficiency virus (HIV) therapies that already use combinations of drugs successfully for overcoming resistance and improving efficacy.[3]

## THE HALLMARKS OF AGING

The nine hallmarks of aging can be considered a framework for describing what occurs during the aging process itself.

### Genomic instability

Genomes can be impacted by various factors, both inside (such as oxidative damage and erroneous replication) and outside (for instance, ultraviolet damage or specific chemicals) of human bodies. As we age, DNA accumulates chemical damage in the form of base pair mutations, as well as chromosome rearrangements and instabilities, which exceeds the advanced repair systems possessed by our cells.[4]

### Telomere attrition

Telomeres are the nucleic acid caps that protect and provide stability to the ends of chromosomes, similar to the plastic ends of shoelaces. When cells divide, their telomeres shorten until they reach a length that is deemed too short by the cell, causing it to treat the DNA as damaged, thus causing either permanent cell cycle arrest (senescence) or programmed cell death (apoptosis). Thus, the gradual shortening of telomeres provides a mechanism (referred to as the mitotic clock) for controlling/limiting the number of times that stem/progenitor cells can replicate – and is therefore important for replenishing tissues.[5]

### Epigenetic alterations

The epigenome is a dynamic layer of chemical modifications (e.g., DNA methylation, histone acetylation) outside of the DNA sequence that modulates how genes are expressed. As we age, we experience significant epigenetic drift, or the gradual movement away from the original, specific pattern of gene expression of our cells (i.e., cellular "identity"). This is reflected in the following: A system-wide loss of DNA methylation (global), the addition of methyl groups to specific locations in the genome (local), leading to silencing of tumor suppressor genes, and modification of the histone proteins that associate with DNA (histone marks). All of these changes contribute to the loss of the smooth and coherent functioning of our cellular machinery, and ultimately to the functional decline of the cell.[6]

### Loss of proteostasis

Proteins have a precise and interconnected system that allows cells to maintain their homeostasis through faithful synthetic production, proper folding, appropriate distribution (trafficking), and appropriate destruction (degradation). The mechanisms in place (the protein quality control system) become ineffective with increased age. As a result, we start to see an accumulation of damaged and/or improperly folded proteins, which can bind together and create toxic aggregates that are implicated in causing the cognitive decline of neurodegenerative diseases (such as amyloid β and α-synuclein) and a lack of efficient cellular function. The decline of autophagy (a process of cellular "self-eating" of damaged proteins) has become a hallmark of aberrant protein aggregation.[7]

### Deregulated nutrient sensing

The cells in our bodies rely on nutrient availability as determined by well-established signaling pathways. Aging affects this ability to sense nutrients and alter metabolism appropriately. Important anti-aging signaling pathways such as AMP-activated protein kinase (AMPK), which is activated by low energy/AMP, and the sirtuins, which are NAD+-dependent deacetylases, become less responsive over time.[8]

### Mitochondrial dysfunction

Mitochondria are thought to be the powerhouses of cells; they produce adenosine triphosphate; however, they have many other functions. The age-related decline in mitochondria is associated with the diminished capacity of oxidative phosphorylation, increased formation of reactive oxygen species, and a reduced ability to undergo turnover (or mitophagy).[9]

### Cellular senescence

Senescence refers to a stable arrest in the cell cycle that occurs when a cell has been damaged or stressed. Senescent cells lose the ability to perform their intended cellular functions, yet they remain alive and metabolically active and thus continue producing a variety of very detrimental biologically active substances such as many inflammatory cytokines, growth factors, and proteases (known collectively as the Senescence-Associated Secretory Phenotype or SASP). The SASP induces significant damage to the tissue microenvironment, drives a state of inflammation that can be chronic (termed "inflammaging"), and has the potential to induce senescence in neighboring cells.[10]

### Stem cell exhaustion

Stem cells are used as a reservoir to regenerate and repair tissues. As we get older, a combination of intrinsic factors, such as epigenetic changes and damage, and extrinsic stressors from the environment, such as the SASP and inflammatory signals, decreases this reservoir.[11]

### Altered intercellular communication

Aging is not solely the result of intrinsic cellular processes; it is also determined by how our bodies communicate throughout time. The aged environment (systemic milieu) is characterized by an increase in inflammation (inflammaging), dysregulation of hormones (i.e., reduced levels of certain hormones), and impairment of neurons in transmitting their signals. All these alterations affect the function of age-healthy cells in an ongoing series of events, creating a self-perpetuating cycle. A great example of the altered, pathological state of communication can be found within the SASP.[12]

## AGING AS A MODIFIABLE CONDITION: THE GEROSCIENCE PERSPECTIVE

The nine hallmarks form an intricate web that leads us to a new idea: The Geroscience Hypothesis. This is the idea that by attacking the underlying molecular foundation of aging itself, we are able to slow down, prevent, or alleviate the effects of all age-related chronic diseases as a collective, rather than as individual conditions that develop one by one after they have developed.[13] It is well established that the greatest risk factor for the majority of diseases responsible for death today is old age, such as heart disease, cancer, Alzheimer's disease, and Type 2 diabetes.[14]

## MOLECULAR PATHWAYS TARGETED BY ANTI-AGING THERAPEUTICS

According to the geroscience hypothesis, there is evidence of multiple, indirectly related, evolutionarily conserved molecular pathways that appear to serve as master regulators of the hallmarks associated with aging. As such, pharmacological means (e.g., nutraceutical company supplements) that target a molecular pathway can alter an organism's overall condition from deteriorating toward maintenance.

### The mechanistic target of rapamycin (mTOR) pathway

Mechanistic target of rapamycin (mTOR) integrates signals from nutrients, growth factors, and energy availability for the purpose of promoting processes associated with protein production and cell growth. mTOR is an important kinase during development; however, in both earlier and later life, there is evidence that hyperactive mTOR signaling exponentially increases the rate of biological aging and decreases lifespan across biological species. mTOR inhibits autophagy by driving cellular senescence and promoting the inflammatory response. The inhibition of mTOR (by the use of rapamycin and its analogs or through dietary intervention) is one of the most potent methods to extend lifespan by providing greater cellular homeostasis, enhancing immune function, and delaying age-related disease.[15]

### The AMPK/sirtuin pathway

AMPK is the counterpart to mTOR. AMPK is activated by low energy levels (increased AMP/ADP), exercise, and caloric restriction and functions as an energy sensor throughout the body as well as a master regulator of metabolic homeostasis. AMPK inhibits mTOR and activates sirtuins, which are a group of NAD+-dependent deacetylases. Sirtuins (primarily SIRT1) are important for stress resistance, genomic stability, mitochondrial biogenesis, and inflammation regulation. Sirtuin activity declines with age due to a decrease in levels of NAD+. Hence, the use of AMPK activators or boosting sirtuin activity (for example, through supplementation with NAD+ precursors such as NMN or polyphenol compounds such as resveratrol) is a main mechanism to produce the same effects as caloric restriction, thus promoting lifespan.[16]

### Insulin/IGF-1 signaling (IIS)

Aging is regulated by the IIS pathway. The IIS pathway detects sugars and growth factors available as food for, or like, the human body and extends life from long-lived worms to mammals. High IIS continues to develop through the first stages of growth and reproduction, whereas low IIS causes acquired immunodeficiency syndrome (AIDS) in long-term maintenance. In the elderly, where it is resistant to insulin, it will develop hyperinsulinemia, which will paradoxically overactivate the downstream signals to promote aging. The ability to modify IIS by lowering its activity so as not to induce diabetes remains one of the primary targets in anti-aging research now; it is also intimately linked to mTOR and AMPK pathways.[17]

### Senolytic pathways

Senolytics are a direct, targeted, and specific approach to target the hallmark of cellular senescence, modulating a specific panel of events, unlike the general pathways mentioned above. Senolytics are pharmacological agents that induce apoptosis (programmed cell death) in senescent cells selectively, through the pro-survival mechanisms associated with the BCL-2 family, p53, and tyrosine kinase signaling pathways. The effects of clearing these "zombie cells" with compounds such as dasatinib, quercetin, or fisetin in animal models (referenced) have demonstrated the ability to diminish the SASP, improve the functionality of tissues, and increase the health span of the organism.[18]

## MECHANISMS OF LYCOPENE, RESVERATROL, AND VITAMIN E AND THEIR ANTI-AGING POTENTIAL

### Comparative overview of the three agents

Lycopene, the most common lipophilic carotenoid, can be commonly found in tomatoes, watermelon, and pink grapefruit. Because of the molecular structure of lycopene, which contains 11 conjugated double bonds, it has one of the best abilities to quench singlet oxygen ($^1O_2$),[19] making it an ideal antioxidant for protection against photoaging or oxidative damage, particularly in lipid-rich environments such as cellular membranes and low-density lipoproteins (LDLs). Lycopene also has other mechanisms to act on oxidative stress, such as promoting the up-regulation of gap junction communication through increasing the level of connexin-43, which results in better coordination of cells, resulting in less chance of uncontrolled proliferation.[20] In addition, lycopene modulates phase II detoxification enzymes through the Nrf2 pathway, thereby increasing the antioxidant capacity of the cell through stimulation of endogenous sources.[21,22]

Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a plant-based phytoalexin produced by grapes, berries, and Japanese knotweed in response to stress. While lycopene's primary role in combating aging is through radical scavenging, resveratrol has limited antioxidant abilities, and its anti-aging effects stem from hormesis. Resveratrol works as a low-dose stress mimetic by stimulating the SIRT1-AMPK-peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) pathway, which is a key component of the longevity network.[23,24] The stimulation of SIRT1 (an $NAD^+$ dependent deacetylase) leads to the deacetylation and activation of PGC-1α, which promotes the biogenesis of mitochondria; deacetylation of FOXO transcription factors enhances cellular resistance to stress; and the deacetylation of p53 modifies the cell death pathway. Resveratrol also suppresses nuclear factor kappa B (NF-κB) signaling, decreasing the expression of pro-inflammatory cytokines, and activates autophagy through mTOR. In addition, resveratrol enhances insulin sensitivity and improves endothelial function, opposing the aging of both the metabolic and vascular systems.[25]

There are a total of eight Vitamin E compounds that are fat-soluble. In the body, α-tocopherol is the most bioactive form of Vitamin E. The primary role of Vitamin E is as a chain-breaking antioxidant due to being embedded in the cell membrane and circulating in lipoproteins. Vitamin E will donate a hydrogen atom to the lipid peroxyl radicals (LOO•), which will terminate the chain reaction of lipid peroxidation that ultimately leads to damage to the integrity of cell membranes and generates reactive aldehydes.[26] When Vitamin E donates a hydrogen atom, it becomes oxidized to form an α-tocopheroxyl radical. The α-tocopheroxyl radical can be recycled back to its active form by using co-antioxidants such as Vitamin C or lycopene.[27,28] α-Tocopherol, in addition to being an antioxidant, also has non-antioxidant roles in that it inhibits the activity of protein kinase C and regulates the expression of several key genes involved in the inflammatory response (including decreasing adhesion molecules such as VCAM-1 and ICAM-1) and regulates the activity of various enzymes (including cyclooxygenase-2 and 5-lipoxygenase).[29]

Lycopene, resveratrol, and Vitamin E all have different roles, but they work together to provide protection against oxidative stress, as shown in Figure 1. Vitamin E is found within the lipid bilayer and neutralizes lipid peroxyl radicals (LOO•), which terminate chains of lipid peroxidation reactions. Lycopene is also lipophilic and supports the antioxidant action of Vitamin E by recycling oxidized Vitamin E, thus extending its protective actions. Resveratrol primarily acts within the aqueous cytosol and activates the master regulators of cellular metabolism and stress resistance, AMPK and SIRT1. This activation has three primary downstream effects: (1) It upregulates the endogenous antioxidant enzymes such as superoxide dismutase and glutathione peroxidase; (2) It induces autophagy for the removal of damaged cellular components; and (3) It promotes mitochondrial biogenesis. All three agents work to inhibit the pro-inflammatory transcription factor NF-κB and thus together suppress the inflammation associated with aging (inflammaging). Collectively, these three agents are depicted in the integrated schematic as being able to produce an anti-aging effect through spatially and functionally coordinated mechanisms across the whole network.

## SIMULTANEOUS TARGETING OF MULTIPLE HALLMARKS OF AGING

Each hallmark represents an important factor that contributes to an individual's overall health. Furthermore, by combining these hallmarks, we can engage with the same network at multiple points, thereby creating a more comprehensive anti-aging effect on the body.

### Mitigating primary damage

All three substances directly counteract genome instability and mitochondrial malfunctioning by minimizing oxidative damage to mitochondrial sections and DNA, along with lipid peroxidation, through their high level of antioxidant capacity.[29,30]

### Enhancing cellular housekeeping

The activation of SIRT1 and AMPK by resveratrol and the induction of autophagy can directly promote the maintenance

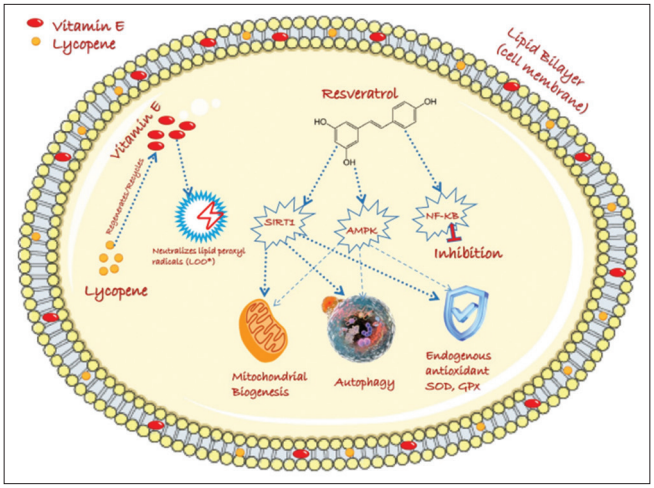



**Figure 1:** Schematic mechanism representation of the complex anti-aging via multiple drug of lycopene, resveratrol, and Vitamin E at the cellular membrane and intracellular signaling level

of the proteome's overall homeostasis and mitochondrial quality (through mitophagy). Vitamin E and lycopene also contribute to the normal function of autophagy-associated membranes and proteasomes by maintaining membrane integrity.

### Modulating signaling and communication

Resveratrol offers a major way of regulating nutrient consumption that is out of balance by modulating both the mTOR and AMPK/SIRT1 pathways negatively and positively, respectively. Each of these compounds also possesses strong anti-inflammatory properties through their ability to block the NF-κB pathway and inhibit the creation of the pro-inflammatory SASP, thereby reversing the effects of altered intercellular signaling and inflammation caused by aging. Finally, by reducing oxidative and inflammatory stress, all three compounds reduce the contributing factors that drive cellular senescence.[31,32]

### Supporting regenerative potential

The prevention of stem cell exhaustion may be indirectly aided by creating a microenvironment that is less inflammatory and has less oxidative stress through this combination. Resveratrol in particular has been shown to enhance stem cell activity and delay replicative senescence in a variety of models.[33,34]

## COMBINATION THERAPIES IN ONCOLOGY AND CHRONIC DISEASES

The rationale for this combination is powerfully supported by the successful application of similar logic in other fields of medicine.

### Oncology

This is the outcome of a shift in focus for the treatment of cancer; it has been a move away from treating cancers with chemotherapy with a single collective agent to using combinations of agents and targeting multiple pathways that will improve control of a patient's cancer (tumor) and decrease the potential for these tumors to develop resistance (with lower doses of each drug).[35]

### HIV/AIDS management

Highly active antiretroviral therapy helped to change HIV from being a fatal disease to a manageable chronic condition using combinations of drugs that act on HIV at different points in its life cycle. This multiple-pronged approach has been effective at suppressing viral replication much better than a single agent and thus preventing any resistance to medications.[36]

### Hypertension and cardiovascular disease

Many hypertension patients will need many different medicines for their first-line therapy to control their blood pressure. This means that they will often take combinations of drugs from at least three different drug classes. These combinations can help give patients better control of their blood pressure with fewer side effects than taking a very large dose of just one class of medication.[37]

## COMBINATION THERAPIES IN MURINE MODELS

Research has moved from looking at individual agents, and so far, studies conducted from this perspective have shown that combining agents that act on multiple aging pathways is more effective than acting on just one aging pathway. For example, rapamycin (an mTOR inhibitor) is known to extend the lifespan of mice. Acarbose (a modulator of glucose metabolism) also extends the lifespan of mice. However, when the two agents are used in combination, the resulting lifespan is more than additive and indicates evidence of a synergistic interaction in male mice.[38] Therefore, using multiple agents that modify two hallmarks of the aging process has greater potential than using a single agent that modifies only one hallmark.

Another significant study involved the use of a senolytic therapy (dasatinib and quercetin) in combination with rapamycin to extend the healthy lifespan in aged mice. While rapamycin extends the healthy lifespan in aged mice as an individual therapy, senolytic therapy eliminates senescent cells, forming and removing the burden of being a senior aged cell having no value as an individual therapy. The benefit of combining these therapies together was that there was more

improvement in physical function of aged mice receiving this combination of agents than from either rapamycin or senolytic therapy alone.[39]

### Triple-agent combinations in model organisms

Three agents can be combined in an identical fashion. The nematode C. elegans is an excellent example where multiple compounds and drugs (resveratrol, quercetin, and metformin) working together resulted in synergy to increase the lifespan of those subjects above that shown using only one of the components alone.[39,40]

### Evidence for the lycopene–resveratrol–Vitamin E combination

While a single, definitive study administering all three compounds together for lifespan is awaited, a wealth of paired and mechanistic evidence strongly supports their combined potential.

- Vitamin E and lycopene: The synergistic effects of lycopene and Vitamin E are extensively documented in preventive disease models. In studies on rodents with prostate or liver cancer, the combination of lycopene and Vitamin E has been shown to be more effective at preventing tumor development as well as slowing progression than either lycopene or Vitamin E alone.[41,42] The mechanism for this effect is thought to be related to their antioxidant properties, which complement one another. In studies of atherosclerosis, lycopene and Vitamin E combined reduce LDL oxidation and inflammation due to plaque buildup to a greater extent than either vitamin alone.[43]
- Resveratrol and Vitamin E: Research has shown that combining a signaling activator and a direct antioxidant works together. In studies examining cognitive deterioration and neurodegenerative processes, the combination of resveratrol and Vitamin E protects neurons better than either agent alone, resulting in improved performance on cognitive tests and decreased markers of inflammation in the brains of research subjects.[44,45]
- Resveratrol and lycopene: Some research has shown that they might also have complementary anti-inflammatory effects. The evidence from in vitro studies indicates that combined use of the three substances may inhibit the NF-kB signaling pathway, which mediates inflammation, more efficiently than each alone.[46]

#### *Molecular and cellular biomarkers*

##### *Epigenetic clocks*

DNA methylation patterns predict biological age. Epigenetic drift (the slow loss of DNA methylation with age) is an exciting target for interventions designed to slow or reverse this process; however, data regarding our specific three compounds are limited, but their targeted pathways are intimately related to epigenetic modification. Resveratrol acts as a direct modulator of histone acetylation and DNA methylation patterns through SIRT1 activation. In both cell and animal studies, resveratrol supplementation has been documented to reverse age-related DNA methylation changes.[47]

##### *Inflammatory markers*

Chronic low-grade inflammation (for instance, "inflammaging") is a well-established indicator of aging as well as being the primary driver of nearly all age-related diseases. There is considerable direct evidence that the combined use of Vitamin E, lycopene, and resveratrol has an impact on this process. All three ingredients have been shown to lower major inflammatory cytokines (such as interleukin-6 [IL-6], tumor necrosis factor-alpha [TNF-α], and C-reactive protein) by tampering with the activation of the NF-κB pathway via the inhibition of oxidative stress-related signaling pathways. In addition, while resveratrol also inhibits NF-κB, it does so by activating SIRT1, which (along with deacetylating and inhibiting the p65 subunit of NF-κB) provides a dual attack on this pathway. In multiple preclinical studies, combinations have consistently produced significantly greater reductions in systemic and local inflammation compared to any one of them alone.[48]

#### *Physical and cognitive functional outcomes*

Ultimately, the value of an anti-aging intervention is measured in preserved function:

##### *Physical function*

In elderly mice, the combination of interventions for increasing NAD+ levels (like resveratrol's ability to have an impact on sirtuins) and antioxidants resulted in a significant improvement in muscle mitochondrial function, which resulted in an improvement in both the ability to exercise and grip strength.[49]

##### *Cognitive function*

There are many ways that oxidative stress and inflammation can negatively impact your brain. The combination of resveratrol and vitamin E demonstrates a synergistic effect when tested in models of cognitive decline, suggesting that there is improved performance in memory tasks associated with significantly higher levels of brain-derived neurotrophic factor and reduced oxidative damage. Neuroprotection provided by lycopene in models of Alzheimer's disease serves to further support lycopene's inclusion.[50]

## CLINICAL EVIDENCE AND TRIALS

Trials on individual and paired components:

### Lycopene

There are several studies that show that high levels of lycopene consumption are associated with lower rates of developing prostate cancer as well as cardiovascular disease and metabolic syndrome. Clinical trials have indicated that taking lycopene supplements significantly lowers oxidative stress and inflammation markers.[51,52]

### Resveratrol

There is human evidence to suggest that taking resveratrol supplements can help improve a person's metabolic health and insulin sensitivity, endothelial function, as well as lower their blood pressure and increase SIRT1 activity and AMPK activity in people.[53]

### Vitamin E

Vitamin E has been studied for decades now, and results from large studies have been mixed. Trials have shown that taking a high dose of α-tocopherol as a single agent can have both positive and negative effects, and that some meta-analyses indicated that high doses may pose risks. However, when Vitamin E is taken with other antioxidants, there is generally less variability in benefit.[54]

### The emergence of geroscience clinical trials

The Targeting Aging with Metformin (TAME) Study, for example, hopes to determine whether or not metformin can help delay some of the common conditions associated with aging, such as diabetes or heart disease. There are also many early senior tests being conducted to evaluate different combinations of senolytic drugs. These are paving the way for further studies related to our proposed combination of ingredients.[55]

## SAFETY AND TOLERABILITY OF COMBINATIONS

An advantage of utilizing combination therapy is being able to use smaller dosages of both agents whilst producing the effects that you want. Based on both the literature review and the previous statements regarding possible combinations, using both agents separately should also provide a safe profile if taken in proper or moderate amounts. Lycopene is considered to be generally recognized as a safe compound according to the U.S. Food and Drug Administration. Studies on long-term use of lycopene have shown no evidence of any adverse effects. Carotenodermia, which is an adverse effect due to extremely high intake levels, has been the only negative effect seen at times.[56] Resveratrol, in human clinical studies of doses between 1 and 5 g/d for long periods, has been shown to be well tolerated with only minor gastrointestinal adverse events (e.g., nausea, diarrhea) reported in most cases. Adverse events, if experienced, appear to be dose-responsive. In these studies, there have been no indications of any long-term adverse events. Safety concerns related to the use of Vitamin E are associated with doses higher than 400 IU/d due to meta-analysis studies that have shown an increased risk of all-cause mortality due to the effects of Vitamin E acting as a pro-oxidant or due to interactions with other fat-soluble vitamins.[57] Vitamin E below 200 IU/d is very safe; however, it should be used with caution in general by the general public. This is especially important for patients taking anticoagulant and/or antiplatelet medications (e.g., warfarin, clopidogrel, and aspirin). Therefore, close medical supervision of patients on polypharmacy, particularly older patients, is important to ensure the safe use of Vitamin E.[58]

## CHALLENGES AND LIMITATIONS

The road from an excellent biological basis to a proven and popular anti-aging remedy is paved with many difficulties. (Table 1). Although the use of a combination of lycopene, resveratrol, and vitamin E is a reasonable and effective approach, there are some difficulties that one should consider. It is not a sign of weakness when discussing the problems; on the contrary, it is a prerequisite to proceeding with research. The following paragraphs highlight the main limitations.[60,61]

### Lack of long-term human data

This fundamental gap in the evidence base is one of the most serious and fundamental issues in this field. Most of the research currently available on combination therapies, including human clinical trials using each ingredient, is short-term (weeks to months) and focuses on measuring specific disease biomarkers for intermediate endpoints; however, the process of aging itself takes many years to fully understand and have longitudinal data collected over many years after administration has occurred. The only way to conclusively determine whether combination therapy can help extend health span by delaying the onset of many diseases and improving functional capacity is by conducting a long-term study involving 5, 10, or even 20 years. Longitudinal studies of this length are extremely expensive, difficult logistically to conduct, and will likely experience high dropout rates. To date, the only trial currently being conducted using the novel methodology of using one prescription drug is TAME. In situations where long-term studies are not feasible, one has to rely on proxy measurements to assess aging. Commonly used proxies include epigenetic clocks, inflammatory cytokines, and physical fitness tests. Although, as we noted in Section 6.4, these types of tools can be useful and valid indicators of age, they cannot replace the true endpoints (i.e., mortality, healthy life expectancy, and quality of life) as a measure of whether or not an intervention provided benefits.[62,63]

**Table 1:** Human biomarker responses to lycopene, resveratrol, and Vitamin E (individual and paired)

| Biomarker category | Specific marker | Lycopene effect | Resveratrol effect | Vitamin E effect | Combination potential |
|---|---|---|---|---|---|
| Oxidative stress | Plasma malondialdehyde/Lipid peroxides | ↓↓ [53] | ↓ [54] | ↓ [26] | Synergistic protection expected, especially in lipid compartments |
| | Urinary 8-OHdG (DNA damage) | ↓ [53] | ↓(Mixed data) | ↓[31] | Combined effect on reducing genomic instability likely enhanced |
| Inflammation | C-reactive protein | ↓↓ [53] | ↓ [54] | ↓ [32] | Complementary inhibition of the nuclear factor kappa pathway suggests strong combined suppression of inflammaging |
| | Interleukin-6, tumor necrosis factor-alpha | ↓ | ↓↓ | ↓ | |
| Metabolic health | Insulin sensitivity (Homeostatic Model Assessment of Insulin Resistance) | Mild ↓ | ↓↓ [25] | Mild ↓ | Resveratrol as primary driver; others may improve adipocyte/muscle membrane health |
| | Low-density lipoprotein oxidation | ↓↓ [44] | ↓ | ↓↓ [44] | Classic synergy demonstrated in Lycopene+Vitamin E trials [53] |
| Vascular function | Flow-mediated dilation | ↑ [59] | ↑↑ [54] | ↑ | Combined improvement in endothelial nitric oxide signaling probable |
| Epigenetic aging | DNA methylation age | Limited data | Emerging ↓ [48] | Limited data | Resveratrol's SIRT1 activation is key; combination may provide optimal milieu for epigenetic stability |

### Individual variability in response

Individual differences exist not only in aging itself but also in how an individual responds to each type of intervention that takes place. The introduction of personalized aging layering adds to the complexity of the subject by introducing variability at every level of consideration.

#### *Genetic makeup*

The individual's genome will determine the metabolism of these substances as well as their place in aging-related pathways. For example, different polymorphisms in the enzymes that metabolize antioxidant substances (i.e., glutathione S-transferase), the enzymes that metabolize drugs (i.e., CYP450 associated with resveratrol), and the pro-inflammatory cytokines (i.e., IL-6 and TNF-α) exhibit tremendous variability between persons with respect to their requirements and responses to these agents. Thus, a highly effective synergistic combination on one person would have little to no effect on another person.

#### *Gut microbiome*

The gut microbiome of humans is important because it is involved in the metabolism of polyphenols such as resveratrol and their activation or inactivation. The gut microbiome composition of a person is influenced by their diet, use of antibiotics, and their environment and may have a large impact on the bioavailability of resveratrol and potentially other compounds to that individual.

#### *Baseline health and lifestyle*

The initial conditions are paramount. Thus, a frail older person with severe inflammatory aging (inflammaging), sarcopenia, and metabolic syndrome would respond with far more intensity to the supplement cocktail than a healthy 40-year-old person. On the other hand, a person consuming an optimal diet high in fruits and vegetables would not receive as great a benefit from supplementation.[64]

## FUTURE DIRECTIONS

The studies of lycopene, resveratrol, and vitamin E are just the beginning of extending health span and are not the end of the scientific journey towards that goal. These three substances can be described as a first-generation, science-based polypharmacology approach. The significance of this research may not only be in terms of its own accomplishments but also in terms of the future potential for personalized anti-aging medicine created by the research. The concept of a "one-size-fits-all" method for addressing the complexities of aging is no longer applicable to this intricate process. In the future, products designed to slow down the aging process will use customized formulations based upon individual aging phenotypes. This will also involve "aging fingerprint" testing to determine whether the aging process in this individual is primarily governed by inflammation (inflammaging), metabolic dysfunction, and depletion of stem cells or senescent cells. For example, a person with a high inflammatory profile would require a unique formulation with high-dose resveratrol and lycopene due to their respective SIRT1/NF-κB and AMP activation functions. Robust instruments are needed to differentiate between different individuals and measure how they differ. By combining every type of multi-omics (genomics, epigenomics, transcriptomics, proteomics, metabolomics, and microbiomics) for individual subjects to

create a picture of that person, it will provide the clearest picture of the biological age and developmental path of any individual. However, artificial intelligence and machine learning used for the analysis of all this data will provide predictive analytic models helping to identify patients with high odds of positive response (via supplementation with a lycopene-resveratrol-vitamin E supplement stack), optimal dosages/availability of supplements, and potentially even identify new individualized supplement formulations. The analysis of physiological data obtained through wearable devices to capture sleep patterns, physical activity, and heart rate variability, with multi-omics data to be able to correlate the physiologic state with the response to supplementation, will also be far easier with the advances in AI and machine learning.

## CONCLUSION

Since there is no way to completely delay aging because the factors that drive the aging process (genomic instability, mitochondrial dysfunction, and inflammatory aging) are interconnected, the use of a single agent will not be successful. Therefore, the combination of lycopene, resveratrol, and vitamin E provides a reasonable strategy for multi-targeting. Each of the three agents offers unique capabilities. Lycopene is a highly effective scavenger of singlet oxygen. Vitamin E is a chain-breaking antioxidant in the lipid membrane and is recycled by lycopene; thus, lycopene extends the useful life of vitamin E. Resveratrol is a signaling compound that activates the anti-aging pathways SIRT1 and AMPK. The three agents work synergistically, not just additively. From a pharmacokinetic perspective, lycopene recycles oxidized vitamin E. From a pharmacodynamic perspective, all three agents work on the NF-kB signaling pathway to exert anti-inflammatory effects via different mechanisms. This triad's value has been demonstrated in a number of studies, including preclinical models and many human biomarker-based studies, showing the triad can improve healthspan. For clinical application, several principles must be followed: dosages should be individualized, considering genetics, the microbiome, and the biological age of the patient; the potential for additive anti-platelet effects must be addressed when taking antihypertensive agents in patients on anticoagulation therapy; and this triad of compounds should be viewed as supportive to lifestyle medicine and not a replacement - especially for individuals who have experienced significant oxidative or inflammatory damage. The investigation of this triad represents a true paradigm shift in the field of geroscience. This is the first "network therapeutic" for anti-aging, showing that it is possible to multi-target the hallmarks. The future of anti-aging pharmaceuticals will be increasingly personalized, dynamic (by the combination of nutraceuticals with senolytics or NAD+ boosters), and holistic (as they will be combined with digital health technologies). Therefore, this combination will not simply be a group of antioxidants but the model for a preventive, global strategy for modulating the biology of aging in order to increase both lifespan AND quality of life.

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