

AGEless Defense

Destroy. Defend. Protect.

A comprehensive 3 pronged approach strategy to deal with AGEs, naturally.

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Abstract

The science and understanding of aging has been expanding at a massive rate over the last decade. Breakthroughs in research in academic institutes and privately held pharmaceuticals are now describing and modelling the process on a molecular level. The identification of key proteins, enzymatic pathways and exo and endogenous biomolecules allows an ever-increasing loci of opportunity to intercede with naturally occurring extracts that have been proven to have a discrete pharmacological effect. We have spent considerable time and effort researching this extensive field which has culminated in the identification of AGEless Defense, a one of a kind product that combats many negative processes associated with the process of aging. We herein report the rationale behind the selection of the individual components of this unique formulation. Advanced glycation end product crosslinking presents one of the challenges facing the population in terms of maximizing health span, and dealing with internal issues which expedite the aging process. AGE crosslinks are extracellular binding between glucose, or sugar, to protein and affect nearly every cell and molecule in the body. While crosslinking is necessary at a cellular level, excess binding results in cells becoming stiffer and more likely to be damaged and subjected to premature aging. While AGEs have predominantly been studied for their role in specific disease models such as predicting cardiovascular disease mortality, or diabetic complications, it has also been proposed by those in the anti-aging community such as Aubrey De Grey and the SENS Research Foundation as one of the main causes of degenerative aging and senescence. While pharmaceutical companies are prevented from allocating funds to research AGEs unless they specifically treat or cure a disease, the nutraceutical industry has simply lacked the initiative to formulate reliable products to address this issue from a preventative manner. Considerable time and effort has gone into selecting and procuring the best available ingredients in dosages sufficient to affect a meaningful result after over a year of consideration. This patent pending proprietary blend of ingredients not only offers the most comprehensive support to both inhibit and break down AGE crosslinks, but deliver powerful results in other more main stream manners such as antioxidant capacity, anti inflammatory results and much more.

Introduction

Advanced Glycation End (AGE) product crosslinking is a naturally occurring physiological phenomena. Many pathological states implicated in age related diseases increase the degree and rate of crosslinking and as such present a challenge to maximizing health and lifespan. AGE crosslinks are formed when binding occurs between sugars (e.g glucose) and lipids or proteins in the intracellular and extra cellular matrix. This affects nearly every cell in the body.

While crosslinking is a natural and necessary physiological process, excessive binding results in cell stiffening which results in them becoming more susceptible to damage and premature ageing. AGE crosslinking has been predominantly studied for its involvement in specific disease models (e.g cardiovascular disease mortality¹ and diabetes)² however, it has also been proposed by the anti-aging community as one of the main causes of degenerative aging and senescence (Aubrey De Grey and the SENS Research Foundation).³

Pharmaceutical companies are prevented from allocating funds to research AGE crosslinking unless they specifically treat or cure a disease, however the nutraceutical industry is not limited by this restriction; it has simply lacked the initiative to formulate reliable products to address this issue, which presents a significant unmet market opportunity.

After more than a year of consideration Natural Wellness Now has selected and procured the best available ingredients and identified dosages sufficient to affect meaningful outcomes. This patent pending proprietary blend of ingredients not only offers the most comprehensive support to both inhibit and break down AGE crosslinks, but also delivers powerful results in other important physiological process associated with aging such as antioxidant capacity and anti inflammation/pro-inflammatory resolution.

About the formulation

Each RDA of AGEless defense provides a carefully derived dosage of the individual ingredients that we believe will maximize results. With efficacy studies set to begin in early 2018 and pending patents filed in Q1 of 2017, our exact formulation is a proprietary blend that limits the opportunity for copy cats. Below we outline the evidence for each ingredient, and why they were selected. By reducing AGEs and their negative affects while simultaneously slowing the formation of new AGEs, AGEless defense offers a comprehensive strategy to reduce the cumulative attack sugar molecules wreak on our bodies,

Individual Components

Rosmarinic Acid

Rosmarinic acid is a caffeic ester of Salvianic acid found in variety of plants. It has significant antioxidant properties and is perhaps the most important ingredient in the formulation. Rosmarinic acid has been shown to have a greater affect at reduction in AGE crosslinks than diabetic nephropathy drug candidate aminoguanidine or Alagebrium.⁴ Aminoguanidine is a clinically tested investigational drug that interacts with 3-deoxyglucosone to reduce the formation of AGEs. Alagebrium is a substituted thiazole drug candidate that was designed to reverse cell wall stiffening by breaking down AGE crosslinks to reduce hypertension and cardiovascular disease. Rosmarinic acid has also shown promising results as a GABA transaminase inhibitor⁵ which could have potential benefits for anxiety disorders and epilepsy. Furthermore, Rosmarinic acid has shown anti viral and anti-inflammatory properties in a mouse model of Japanese encephalitis.⁶ Despite these many and varied benefits, Rosmarinic acid is widely unknown as a supplement, and brands that purport to carrying it often list it as ‘currently unavailable’.

CurcuWIN

Curcumin is a diarylheptanoid from the curcuminoid group of chemicals. It is a bright yellow compound found in turmeric and has a diverse pharmacology. However, its use is limited by poor oral bioavailability meaning that to be efficacious, more than two grams are required daily. This limitation is circumvented with the introduction of CurcuWIN, a highly bioavailable, water soluble curcuminoid. In a “first of its kind” human clinical trial, CurcuWin has been shown to have an increased relative absorption of total curcuminoids by a factor of 46x over standard curcumin. In addition to its antioxidant and anti inflammatory properties, curcumin has also been shown to prevent the negative affects of AGE formations, specifically by countering AGE formation suppression of the Nrf2 pathway via RAGE induced gene expression of leptin and its receptors. Suppression of the Nrf2 pathway leads to increased oxidative stress which curcumin negated in a 2014 study.⁷

L-Carnosine

L-Carnosine, an imidazole containing dipeptide formed by beta-alanine and histidine, is a naturally occurring compound found in red meat. This biologically active and important compound has beneficial antioxidative effects (ref) but more importantly helps prevent AGEs from forming by acting as an antiglycating agent.^{8,9,10} L-Carnosine has also been shown to reduce cellular senescence in a 96 patient trial in patients with cataracts, demonstrating an 80% success rate in advanced senile cataracts and a 100% success rate in patients with mild to moderate cataracts over the 6 month trial period.¹¹ Carnosine is known as a geroprotector (i.e a compound

that can address the root causes of aging and consequently prolong life), it can also reduce the telomere shortening rate (reference)

Bilberry Extract

Bilberry extract is included both for its own benefit in fighting AGEs, and also to complement L-Carnosine. One trial has shown that the combination of carnosine and blueberry extract *in vitro* increased stem cell proliferation *in vitro* by 86%.¹² Bilberries are a closely related Northern European berry that have a similar composition to blueberries, and often show much higher levels of vitamins and anthocyanin, anthocyanin being involved in glucose and lipid metabolism¹³ and showing to effectively prevent the formations of AGEs by trapping methylglyoxal¹⁴. It has also been suggested that bilberry can lower blood glucose levels¹⁵ and the naturally occurring flavonoids found in Bilberries such as Rutin and Quercetin have been found to inhibit various stages of AGE formation.^{16,17} Oxerutin, a hydroxyethyl acetylation of rutoside(rutin) has shown to work in conjunction with Taurine, also found in this formula, was found to be significantly more effective in a rodent model of diabetes resulting in reduced accumulation of collagen-linked fluorescence in skin¹⁸

L-Taurine

Taurine is a product with wide public awareness due to its heavy supplementation and use in the energy drink market. A little-known benefit of L-Taurine is its ability to abolish fructose driven crosslinking in collagen; Fructose has been shown to be a more potent glycation agent than glucose *in-vitro*.¹⁹ Furthermore it has been postulated that diabetic crosslink formations could be largely attributed to fructose *in-vivo*. Our current consumer climate is inundated with high fructose corn syrup as a sweetening agent, and L-Taurine presents itself as an important preventative supplement to completely decimate AGE crosslinks caused by fructose consumption.²⁰

Alpha Lipoic Acid (ALA)

ALA's potential role in AGEs is complicated; ALA has been shown to protect against 4-hydroxynonenal (HNE) mediated oxidative stress and neurotoxicity, making it a potential adjunct therapy for Alzheimers.²¹ HNE is a toxic and reactive alpha,beta unsaturated aldehyde formed by lipid peroxidation in cells with implication in neurodegenerative diseases, various cancers, diabetes and chronic inflammation²². HNE, as a reactive carbonyl species can lead to the following AGEs: N^ε-carboxyethyllysine, arginine pyrimidine, pentosidine, pyrrolin, methylglyoxal, glyoxal lysine and N^ε-carboxymethyllysine.²³ ALA can mitigate AGE formations while simultaneously providing other benefits. Lipoic acid has also shown to prevent collagen abnormalities in high fructose diets in rats.²⁴ In Germany, ALA is prescribed as a drug to treat diabetic neuropathy.²⁵

Benfotiamine

Benfotiamine is a synthetic derivative of Vitamin B1 and though classified as a drug in many countries around the world it is available as a supplement in North America and Canada. It has been studied as a possible treatment for diabetic nephropathy²⁶, retinopathy²⁷ and neuropathy²⁸. Benfotiamine is an AGE formation inhibitor, and has been shown to significantly attenuate the formation of AGEs and collagen crosslinking.²⁹

Vitamin C

Vitamin C needs no introduction. Perhaps the most widely studied and supplemented product, ascorbic acid has also shown promise in fighting AGEs by decreasing serum protein glycation³⁰³¹ More than its antioxidant activity it is a required cofactor for collagen synthesis and other critical enzymatic functions.³² AGEless Defense ensures that customers receive above the RDA of Vitamin C for all the bodies needs, while contributing to our multi prong Destroy, Defend and Protect strategy to deal with AGEs.

Vitamin B6

Vitamin B6 has been heavily studied for its' potential role in advanced glycation end products and has shown evidence for efficacy in all common forms, such as pyridoxine³³³⁴³⁵, pyridoxal³⁶³⁷ and pyridoxamine³⁸³⁹⁴⁰ In 2009, the FDA ruled pyridoxamine an illegal form of vitamin B6 due to it being the only active ingredient in Biostratum's diabetic nephropathy drug Pyridorin, following a several year successful lobbying campaign by Biostratum.⁴¹⁴² Fortunately, pyridoxine and pyridoxal remain available to the public with pyridoxine showing benefits alongside lipoic acid also found in this formulation(ref 16). Additionally, pyridoxine has also show improvements in diabetic patients with symptomatic peripheral neuropathy when used in conjunction with Vitamin b1, also found in this formulation⁴³. Vitamin B6 acts as a coenzyme function in roughly 100 enzyme reactions in glucose, amino acids and lipid metabolism.⁴⁴ Cinnamaldehyde has also shown to exhibit anti inflammatory and neuroprotective effects.⁴⁵

Clove and Cinnamon

The addition of clove and cinnamon are important in that they contain high levels of eugenol in both spices, and cinnamaldehyde in cinnamon. Eugenol, in addition to being an anti inflammatory via inhibition of prostaglandin synthesis⁴⁶⁴⁷ has also shown to potentially have a dual role in inhibition of AGEs⁴⁸ Cinnamaldehyde has likewise shown to attenuate AGEs by the suppression of AGE-induced biological responses mediated by inactivating the JAK2-STAT1/STAT3 cascade or activating the NO pathway.⁴⁹

Resveratrol

Resveratrol is one of the most hyped and marketed putative anti-aging supplements to emerge in the last few decades and has been studied for its implications in life span, cancer, metabolism, cardiovascular issues and neurodegenerative issues. Its potential for reducing AGEs is less well reported however. A recent study found that Resveratrol inhibits AGEs induced proliferation and collagen synthesis activity.⁵⁰ Resveratrol also shows positive results in studies pertaining to diabetes such as its effect in type II diabetic rats.⁵¹

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