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Original article

Modulation of infection-induced inflammation and locomotive deficit and longevity in senescence-accelerated mice-prone (SAMP8) model by the oligomerized polyphenol Oligonol

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Abstract

Oligonol is produced from the oligomerization of polyphenols (typically proanthocyanidin from a variety of fruits such as lychees, grapes, apples, persimmons, etc.) and contains catechin-type monomers and oligomers of proanthocyanidins. The ability of Oligonol to affect infection-dependent eye inflammation, locomotion and longevity in senescence-accelerated prone mice (SAMP8) (a model of senescence acceleration and geriatric disorders with increased oxidative stress and neuronal deficit) was investigated. Oligonol (60 mg/kg) significantly modulated the extent of inflammation scores in the eye of SAMP8 mice. Examination of the mice indicated infection with mouse hepatitis virus and pinworm (*Syphacia obvelata*) in both males and females and with the intestinal protozoa (trichomonad) in males. A comparison of the two groups (using log-rank test) and the difference in the mean life span between groups (using Student's *t*-test) indicated significant differences in survival ($p = 0.043$) and the mean life span ($p = 0.033$) in male SAMP8 mice. Oligonol increased the mean life span and this was statistically significant. In the open-field locomotive test, the 7-week-old SAMP8 mice crossed more than 40 partitioned lines in 1 min. At 48-week-old control untreated male SAMP8 crossed 2 lines. The Oligonol-treated 48-week-old male SAMP8 mice crossed 17 lines however. The improved locomotive activity was statistically significant even after 36 weeks in the Oligonol-treated male SAMP8 but this was not the case throughout the time course of the study in the Oligonol-treated female SAMP8. Thus Oligonol treatment to SAMP8 mice modulated the severity of infection-dependent inflammation, prolonged life-span and significantly improved locomotive activity indicating potential benefit to aging-associated diseases such as Alzheimer's or Parkinson's diseases. This presents potential for further research to define infection-dependent inflammation associated with degenerative conditions and the molecular mechanism of dietary antioxidant protection.

Keywords: Oligonol; Senescence-accelerated mouse; SAMP8 mice; Anti-aging; Anti-infective agents; Infection and inflammation; Oxidative stress; Open field test; Redox signaling; Parkinson's disease; Alzheimer's disease; Movement disorders; Behaviour deficits; Longevity

1. Introduction

The aging-associated diseases (Alzheimer's disease (AD), Parkinson's disease (PD), cancer, amyotrophic lateral sclerosis (ALS), atherosclerosis, myocardial infarction, rheumatoid arthritis and type 2 diabetes) are underpinned by chronic inflammatory mechanisms [1–6]. The extent to which this chronic inflammation (whether a primary or secondary causal event) influences the pathogenesis, progression and prognosis of these diseases is continually being understood, and in the same vein, driving the search for prophylactic agents that can counter inflammatory reactions [5,7–9].

Chronic inflammatory conditions are often associated with local infiltration of inflammatory cells, such as macrophages, and higher circulatory levels of pro-inflammatory cytokines, complement components and adhesion molecules [10], redox biochemistry and cell signaling cascades. The impact of

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systemic infection on the progression of neurodegenerative disease [11] has continued to receive attention from the standpoint that systemic infections exacerbates the inflammatory response in the central nervous system which impacts on neurological functions [6,11]. Free radical theory of aging [12] holds the view that aging and its related disease processes are the net consequence of free radical-induced damage and diminished antioxidant defenses. Old people have to cope with a lifelong antigenic burden that encompasses several decades of evolutionary unpredicted antigenic exposure. This chronic antigenic stress and the subsequent inflammatory burden may have a major impact on survival and frailty [2]. However, the generation of reactive oxygen and nitrogen species (ROS and RNS) activates redox sensitive transcription factors leading to the generation of pro-inflammatory molecules and a state of chronic inflammation. This oxidative stress and subsequent chronic inflammation have been implicated as mediators of almost all of the aging-associated diseases [1,10,13,14].

Oligonol (Fig. 1) is an oligomerized phenolic product containing catechin-type monomer and oligomer of proanthocyanidin. The contents of oligomers in a typical polyphenol polymer can be less than 10%. Typically the constituents of Oligonol are 15–20% monomer, 8–12% dimer, and 5–10% trimer [15–17]. The safety and toxicology of Oligonol has been extensively studied and found to be safe with LD50 in rats of 5.0 g/kg body weight. This corresponds to a dose of 300 g for an average human with a 60 kg body weight [15,16]. Supplementation of rats with Oligonol prior to the administration of ferric-nitrilotriacetic complex (a Fenton chemistry model) significantly reduced the extent of lipid peroxidation in the kidney, brain and liver, indicating in vivo antioxidant potential [15]. Oligonol triggers apoptosis in MCF-7 and MDA-MB-231 breast cancer cells through modulation of the pro-apoptotic Bcl-2 family of proteins and the MEK/ERK signaling pathway, an observation suggesting its important chemopreventive effects [18]. Oligonol modulates the Aβ-induced oxidative insult and dysfunction in mitochondrial membrane integrity in PC12 cells indicating potential neuroprotection functions [19]. The general consensus of opinion is that the beneficial health effects of flavonoids are determined by their bioavailability, bio-accessibility functions that are, in turn, dependent on their structure and structural integrity. Catechins have found uses as naturally available antioxidants in oils and fats against lipid peroxidation, supplements for animal feed to improve animal health and protect animal products, antimicrobial agents, in foodstuffs and dietary supplements [15,20–24]. This presents scope for the application of Oligonol.

The senescence-accelerated mouse (SAM) is an accelerated aging model that was established through phenotypic selection from a common genetic pool of AKR/J strain of mice and includes nine major senescence-accelerated mouse prone (SAMP) substrains and three major senescence-accelerated mouse resistant (SAMR) substrains, each of which exhibits characteristic disorders and SAMP8 are now increasingly used in gerontological research due to its characteristic learning and memory deficits at old age [14,25]. Senescence of function is widely believed to underlie the decrease in quality of life in addition to the increase in susceptibility to disease and death associated with aging, identifying the mechanisms involved would be highly beneficial [14,26]. The ability of Oligonol to modulate inflammation in SAMP8 mice was investigated. It was also of interest to ascertain if treatment with Oligonol can modulate the debilitating age-dependent locomotive deficit using the open field test [27,28] and affect SAMP8 survival in both males and females.

2. Materials and methods

2.1. Source of Oligonol

Oligonol® (Fig. 1) (>95% purity) (Amino Up Chemical Company, Sapporo, Japan) was obtained from a patented technology process (WO 2004/103988 A1). Briefly, the process involves the extraction of powdered dried fruits with aqueous ethanol. The concentrate was subjected to a DIAION HP-20 column and eluted with aqueous. This was washed and evaporated to dryness yielding a dark brown powder consisting of a mixture of proanthocyanidins. The resulting mixture was combined with L-cysteine hydrochloride monohydrate and

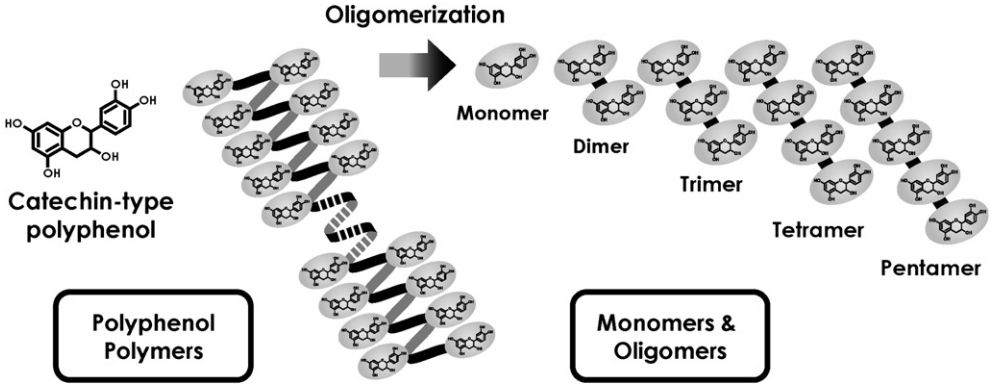

Fig. 1. Structural concept of Oligonol. The structures of the major components of Oligonol have been confirmed by mass spectrometry and nuclear magnetic resonance spectroscopy analysis to be derivates of procyanidins B1 and B-2, epicatechin-(4β-8)-epicatechin-(4-β-8)-catechin and epicatechin-(4β-8)-epicatechin-(4-β-8)-epicatechin.