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COMMENTARY

L-Fucose is a promising gerotherapeutic drug

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Abstract

Current testing of anti-aging therapeutics has relied heavily on the ability of a candidate compound to extend lifespan in animal models, with less emphasis on enhancing resilience to aging and increasing health span. The consequences of this approach mean many clinically relevant compounds will be missed. An example is L-Fucose, which is a single-ring sugar found as the primary component of fucoidan concentrated in brown seaweed. Despite the lack of dedicated studies to determine effect of L-Fucose on lifespan, examination of the literature and unpublished observations show L-Fucose successfully modulates multiple pathways of aging. These include a reduction in inflammation and reactive oxygen species, enhanced lipid metabolism and wound healing, as well as modulating phenotypes in models of neurodegenerative disease and cancer. In addition, L-Fucose is orally bioavailable and well tolerated. Due to the diverse and robust effects of L-Fucose, its inclusion in single or combinatorial gerotherapeutic studies on aging interventions should be strongly prioritized.
Keywords: Gerotherapeutic, L-fucose, aging intervention, resilience to aging, health span, aging pathways

Aging is a complex and multifaceted process. While any one hallmark of aging may have antagonistic effects on other hallmarks, it isn't a surprise that categorizations of gerotherapeutic drugs have begun to form distinct groupings based on their potential to address and modulate specific aging pathways. Several examples highlighted from the Albert Einstein College of Medicine include mTOR inhibitors, GLP-1 agonists, SGLT2 inhibitors, and bisphosphonates among others [1]. Programs studying these compounds tend to prioritize the potential to extend lifespan, with less emphasis on compounds capable of enhancing resilience to aging. L-fucose is a candidate compound that fits in the latter category and is worthy of rigorous testing as a gerotherapeutic drug. It is generally considered safe and is well tolerated, orally bioavailable, and crosses the blood brain barrier via GLUT1, a glucose transporter [2].

L-fucose is a single-ring biologically relevant sugar found primarily as a component of fucoidan in brown seaweeds. It is the necessary substrate for fucosylation performed by fucosyltransferases. Fucosylation regulates a number of developmental processes and cellular metabolism through the attachment of GDP-fucose to different glycans and glycoproteins, all of which have been well documented [3]. Current examination of L-fucose has primarily focused on its anticancer properties, for which is has been shown to slow tumor growth in melanoma, carcinoma, and colon cancer models [4-7]. Even more impressive, recent studies have revealed strong evidence of multiple age-related pathway effects, which support the implementation of L-fucose as a gerotherapeutic.

L-fucose has been shown to modulate inflammation across organ systems. In mice with lipopolysaccharide (LPS)-induced inflammation, treatment with L-fucose decreased macrophage activation in the gut and microglia activation in the brain [8, 9] whereas decreased levels of L-fucose were shown to be associated with increased microglial-driven inflammation through cytokine sensitivity [10]. In another study, inflammatory markers IL-6, MCP-1, and TNF-alpha had significantly less expression when a high-salt diet was paired with L-fucose. It was found in comparison of knockout Muc2 mice and controls that Treg cell activation was responsible for a decrease in inflammation in the gut [11]. Pathway analysis from these studies showed L-fucose significantly inhibited the activation of the JAK2-Akt-STAT3 pathway.

L-fucose has been reported to decrease reactive oxygen species. Polysaccharides containing high compositions of L-fucose have been shown to scavenge reactive oxygen

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species and prevent cell death through modulation of the anti-apoptotic Becl2 and inhibited MAPK pathways [12]. In another study with L-fucose-rich polysaccharide, it was found that cell morphology and cell viability were preserved along with a reduction in reactive oxygen species [13]. Additionally, low doses have been shown to protect against ascorbate-induced reactive oxygen species cell death [14].

L-fucose has previously been proposed as an anti-obesity compound. In a study of mice fed a high fat diet, L-fucose significantly prevented weight gain and an increase in fat mass. Additionally, treatment with L-fucose prevented the development of hepatic steatosis and restored dysbiosis in the gut [15]. Mice fed a high calorie diet and treated with L-fucose showed a dose-dependent prevention of weight gain and adipose gene expression [16]. Another related study in mice showed that L-fucose upregulated the AMPK pathway, responsible for fatty acid oxidation and lipolysis, in adipocytes preventing the accumulation of lipids as well as increased glucose uptake in an insulin-resistant state [17].

L-fucose has been reported to enhance wound healing. Using dermal injury as a model of wound healing in rats, treatment with Low-Molecular Weight fucoidan revealed increases in TGF-beta, VEGFR-2, MMP9 along with accelerated wound healing [18]. Other studies have demonstrated accelerated wound healing using l-fucose in corneal injury and amelioration of diabetic injury of the enteric nervous system [19, 20].

Several studies have suggested that L-fucose may have potential as a treatment for neurodegenerative diseases. L-fucose was reported to alleviate cognitive impairment in the 5xFAD mouse model of Alzheimer's disease through rescue of excitatory neurons [21]. Findings showed decreased levels of neuronal L-fucose resulting in a possible phenotypic treatment. Another study suggested that fucoidan may be a possible treatment for Parkinson's disease. Treatment in a mouse model of Parkinson's demonstrated reduced neuronal loss, improved mitochondrial function, and improved motor function [22].

In conclusion, L-Fucose is a promising gerotherapeutic compound based on its bioavailability and safety, and its antioxidant, anti-inflammatory, anti-cancer, and enhanced lipid metabolism properties. It has a demonstrated ability to effectively modulate age-related phenotypes in animal models. The high potential for enhancing resilience to aging and increasing health span necessitates its consideration for aging intervention studies to justify clinically relevant investigations.

Declarations

Availability of data and materials: Not applicable.

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