Review of: "Hyphae and Healthspan"

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Potential competing interests: No potential competing interests to declare.

The study entitled “Hyphae and Healthspan” presents a complex and multifaceted argument linking Candida overgrowth (CO) to a wide array of health issues, ranging from autoimmune diseases and viral reactivation to chronic inflammatory conditions. While the hypothesis is ambitious and thought-provoking, it suffers from several critical issues, particularly regarding the clarity of the connections made, the empirical support for the claims, and the coherence of the overall narrative. Below is a detailed critique of the key elements presented in this study:

1. Introduction

* The introduction suggests a causal link between Candida and a wide range of systemic diseases, including autoimmune disease, cancer, dementia, and atherosclerotic cardiovascular disease (ASCVD). However, the mere presence of Candida in individuals with these conditions does not necessarily imply that Candida is a causative factor. For example, while periodontitis (an oral disease often associated with bacterial infections) has been linked to systemic conditions like cardiovascular disease, the role of Candida in this process is far from clear. The introduction would be more scientifically rigorous if it distinguished between correlation and causation and acknowledged the need for more research to clarify these relationships.

* The introduction presents Candida as a primary villain in the deterioration of healthspan, without adequately considering the broader context. It would be more balanced to acknowledge that while Candida can contribute to health problems, it is typically kept in check by a healthy immune system and gut microbiome. In most individuals, Candida exists as a commensal organism, meaning it lives in the body without causing harm. It is only when the immune system is compromised, or the microbiome is disrupted, that Candida may overgrow and cause problems. This more nuanced view would provide a better foundation for discussing the conditions under which Candida becomes pathogenic.

2. Discussion:

* The discussion attempts to link a wide array of diseases, such as autoimmune diseases, dementia, cancer, and cardiovascular diseases, to periodontitis and Candida overgrowth. While there is evidence supporting the connection between periodontitis and systemic diseases like cardiovascular disease and rheumatoid arthritis (RA), the extension of this to Candida overgrowth as a central pathogenic factor is less substantiated. The complexity of the relationships presented, including the involvement of the NLRP3 inflammasome, zonulin, and Gq coupled GPCR antibodies, creates a narrative that is difficult to follow and may be overly speculative.

* The assertion that Candida overgrowth plays a pivotal role in periodontitis, potentially even preceding and potentiating the growth of periodontopathogenic bacteria like *Porphyromonas gingivalis*, is an interesting hypothesis but requires more robust evidence. Candida species are indeed found in the oral microbiome and can be associated with oral diseases like thrush and periodontitis, especially in immunocompromised individuals. However, the idea that Candida is a primary driver of periodontitis, particularly in individuals without clear immunodeficiency, extends beyond what the current literature supports.

* The discussion attempts to explain the role of candidalysin in inducing citrullination, leading to the production of anti-citrullinated protein antibodies (ACPAs) and cyclic citrullinated peptide antibodies (CCPAbs), which are implicated in autoimmune diseases like rheumatoid arthritis (RA) and severe COVID-19. However, the mechanistic pathway proposed is complex and lacks clear, step-by-step evidence that Candida and candidalysin specifically drive these processes.

Citrullination and the formation of ACPAs are indeed key processes in RA and other autoimmune diseases, and there is evidence linking certain infections (like *Porphyromonas gingivalis*) to citrullination. However, the direct role of Candida and candidalysin in this process is not as well-established. The discussion would benefit from citing specific studies that demonstrate how candidalysin directly leads to hypercitrullination and the subsequent formation of ACPAs in humans.