REVIEW ARTICLE

IJBCS
Indones J Basic Clin Stud. 2026; 1(2): 94-101
doi: 10.18585/ijbcs.v1i2.31

Nutrigenomic Pathways in Okinawan Longevity: Distinguishing Molecular Mechanisms from Population-Level Associations

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Molecular hallmarks of aging, such as telomere shortening, genomic instability, and the loss of proteostasis, significantly elevate susceptibility to age-related chronic diseases and mortality. Targeted dietary interventions represent a non-invasive strategy to modulate these hallmarks and extend health-span. The traditional Okinawan diet, characterized by low-caloric density and high phytonutrient content, has long been associated with exceptional longevity, yet the precise nutrigenomic pathways remain to be fully elucidated. This review aims to synthesize current evidence on the molecular mechanisms through which the Okinawan diet promotes longevity, specifically focusing on its ability to distinguish direct nutrigenomic pathways such as the modulation of FOXO3 and SIRT1 genes, from broader population-level associations. A systematic literature search was conducted via the PubMed database using the primary search term "Okinawan diet." The selection criteria focused on peer-reviewed articles published up to 2026, specifically targeting studies that explore molecular markers, gene expression (e.g., FOXO3, SIRT1), and longitudinal health outcomes in both human cohorts and experimental models. Evidence indicates that specific Okinawan dietary constituents, such as purple sweet potato anthocyanins and seaweed-derived fucoidans, act as potent signaling molecules. These components up-regulate FOXO3, enhancing cellular stress resistance, and activate SIRT1, which promotes DNA repair and metabolic homeostasis. These findings suggest that the Okinawan phenotype is not merely a result of caloric restriction but is driven by specific nutrient-gene interactions that delay cellular senescence. The traditional Okinawan diet demonstrates significant potential as a nutrigenomic model for healthy aging. While population-level data provide a strong foundation, the transition toward personalized nutrition based on genetic profiling is essential. Future research must prioritize longitudinal human trials to further distinguish correlative observations from definitive causal nutrigenomic mechanisms.

Keywords: aging, diet, longevity, okinawan, nutrigenomics

Introduction

Aging is an intricate process observed at the molecular, cellular, tissue, and systemic level that is inevitable for all living organisms.[1] Aging is characterized molecularly by genomic instability, which is the accumulation of damage to the genome over time, as seen in DNA strand breaks, point mutations, deletions, insertions, and alterations in chromosome structure.[2] Other indicators of aging at the molecular level include telomere shortening, epigenetic alterations, and loss of proteostasis ability. Evidence of aging may be observed at the cellular level in cellular senescence, mitochondrial dysfunction, and deregulated nutrient sensing. Ultimately, these molecular and cellular changes can cause

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Submitted: 9 Juli 2025
Last Revised: 23 April 2026
Accepted: 7 May 2026

stem cell exhaustion, impaired intercellular communication, chronic inflammation, and dysbiosis, which results in an aging phenotype.[3] In many chronic disorders that contribute to mobility and mortality, this aging condition is frequently the most important risk factor.[1] In Indonesia, mortality data for chronic or non-communicable diseases accounted for 73% of all fatalities, with the following breakdown: cardiovascular disease (35%), cancer (12%), chronic respiratory disease (6%), diabetes (6%), and and the risk of premature death is more than 20%.[4]

According to the projections for Bappenas, the aging population in 2025 is 35.45 million and is expected to reach 57.26 million by 2040.[5] With an increasing elderly population, it is important to anticipate the occurrence of non-communicable diseases in the elderly and reduce the risk of death by implementing a healthier lifestyle. A healthy lifestyle is expected to help the healthy aging process and increase life expectancy. In addition, the perception and management of chronic diseases play an important role in successful aging. Research shows that older adults who have better control and understanding of their chronic conditions report higher levels of optimism, life satisfaction, and successful aging.[6] This is in line with Sustainable Development Goals (SGDs) number 3 which aims to reduce premature deaths from non-communicable diseases by a third by 2030. Achieving this target could significantly increase life expectancy, with a potential increase in life expectancy of between 30 and 70 years. This goal emphasizes the importance of effective prevention, early detection and treatment programs tailored to major non-communicable diseases.[7]

Okinawa Prefecture in Japan serves as an illustration of how a population may have a long life expectancy and a low prevalence of chronic illnesses. The people in this population follow a particular way of life and diet. The traditional Okinawan diet prioritizes calorie restriction, a diverse range of vegetables and nuts rich in minerals, vitamins, and polyphenols, and meals low in salt.[8] Recent research has demonstrated that diets rich in polyphenols can lower the risk of developing a variety of age-related diseases, as well as enhance a number of age-related health outcomes, including changes in lipid profiles, endothelial dysfunction, high blood pressure, insulin resistance, and cognitive impairment. Other studies have demonstrated that centenarians regularly consume polyphenols as part of their diet, which has geroprotective properties. Numerous indications of aging are impacted by this phenomenon, including telomere length, mitochondrial dysfunction, and cellular senescence.[9]

Nutrigenomics is the branch of science that investigates how the Okinawan diet affects gene expression at the molecular level. This area allows us to examine how specific nutrients can change gene activity or expression, as well as how genetic diversity influences our reactions to various diets and foods.[10] Genistein, one of the isoflavone components found in soybean seeds that is frequently consumed by Okinawans, is known to influence epigenetic processes by affecting DNA methylation and histone modification. These epigenetic alterations have an impact on gene expression, cellular identification, and general health throughout one's lifetime. Genistein is well known to bind to the catalytic region of DNA methyltransferase 1 (DNMT1), which reduces the methylation capacity of tumor suppressor genes. Moreover, genistein has the ability to enhance histone acetylation at the promoter regions of particular genes implicated in apoptosis and cell cycle control.[9] Although the health effects of isoflavones, including genistein, have been well documented, there are various other phytochemicals that are part of the Okinawan diet that play a significant role in contributing to cellular longevity. For this reason, this article attempts to explore the complex interplay between the entire dietary composition of the Okinawan diet and specific gene expressions involved in aging processes. This review proposes an innovative perspective by shifting from the general epidemiological observations to a more detailed molecular perspective. This review is distinct from previous research in its explicit distinction between the direct nutrigenomic effects and population-based correlations, along with an explanation of the mechanism through which phytonutrients from Okinawan affect longevity.

Methods

A systematic literature search was conducted using the PubMed database through April 2026. The search strategy employed a combination of targeted keywords, including “Okinawan diet”, “longevity”, “nutrigenomics”, and specific genetic regulators such as “FOXO3” and “SIRT1”. The focus was strictly maintained on studies linking traditional dietary patterns to the molecular mechanisms of aging. The review incorporated longitudinal observational studies of the Okinawan population alongside experimental research involving animal or cellular models. Inclusion

required empirical data on the interactions between specific bioactive compounds (e.g., anthocyanins, fucoidans) and gene expressions associated with cellular survival, stress resistance, and metabolic homeostasis. Data were synthesized by distinguishing population-level correlations from causal evidence derived from laboratory interventions. To minimize sampling bias, the analysis explicitly separated data from the traditional Okinawan cohort and the modernized population. This distinction ensures that the identified molecular pathways accurately reflect the authentic longevity phenotype rather than confounding environmental factors.

Results and Disscussion

The traditional Okinawan diet is known to contribute significantly to improving health and life span of the people in Okinawa. The key characteristic of the traditional Okinawan diet is summarized and compared with the Western diet in **Table 1**. This comparison highlights differences in macronutrient composition, dietary quality, eating behavior and associated molecular effects related to aging and metabolic health. Overall, the traditional Okinawan diet represents a low-calorie, nutrient-dense, plant-based dietary pattern enriched with bioactive compounds that favor longevity-associated molecular pathways, in contrast to the Western Dietary pattern characterized by high energy density, saturated fat, and pro-inflammatory profiles.[11,12]

Fundamentals of Okinawan Diet Nutrigenomics

The traditional Okinawan diet has a significant effect on nutrigenomics. Nutrigenomics is the study of the interactions between food and genes. This field helps us understand how specific nutrients can alter gene activity or gene expression, as well as how genetic variations influence responses to certain foods and diets.[10] The traditional Okinawan diet, which contains colorful vegetables, medicinal spices, and seafood rich in fucoxanthin and astaxanthin, can activate the Nuclear factor erythroid 2–related factor 2 (Nrf2) pathway. This pathway regulates the expression of antioxidant genes and genes involved in detoxification, as protection against oxidative stress. Other food components, such as soybeans high in isoflavones and tea that rich in polyphenols, can activate the Forkhead Box O3 (FOXO3) gene. This gene is a key transcription factor in the insulin and insulin-like growth factor-1 (IGF-1) signaling pathways, enabling the body to regulate metabolism and repair Deoxyribonucleic acid (DNA) damage, thus extending cellular lifespan. The FOXO3 gene is activated by calorie restriction, which is implemented in the Okinawan diet. Foods such as purple sweet potatoes, turmeric, and seaweed act as caloric restriction mimetics that help improve metabolic regulation.[14]

Additionally, active polyphenol compounds such as curcumin and resveratrol are able to regulate the activation of the Sirtuin (SIRT1) gene, which is involved in energy metabolism and cell repair. Foods like bitter melon also contain hormetic phytochemicals that activate the body's adaptive mechanisms, enhance resistance to cellular aging, and reduce the risk of degenerative diseases.[14] The Okinawan diet also regulates metabolism through gene expression. For example, bitter melon contains compounds such as charantin and polypeptide-p that modulate glucose metabolism, while fucoxanthin found in seaweed influences genes related to fat burning and energy metabolism, thereby helping to prevent diabetes and obesity.[18] The antioxidant and anti-inflammatory compounds in this diet also play a role in epigenetic regulation, which refers to how the environment or food influences gene expression without altering the DNA structure. For example, curcumin in turmeric can affect gene expression by inhibiting histone deacetylase enzymes, thereby helping to prevent inflammation and abnormal cell proliferation. Broadly speaking, the Okinawan diet is also capable of lowering levels of pro-inflammatory cytokines such as Interferon gamma (IFN-γ), Interleukin (IL)-17a, Monocyte chemoattractant protein (MCP)-1, and Inducible protein (IP)-10, indicating that this diet can modulate the expression of genes involved in inflammation.[11, 18]

Another study mentioned the nutrigenomic effects of the traditional Okinawan diet, including an increase in 1,5-anhydroglucitol, which reflects improved short-term glycemic control, and a decrease in chiro-inositol, which influences insulin sensitivity. Additionally, the Okinawan diet can alter the composition of gut microbiota, as evidenced by an increase in beneficial bacteria such as Akkermansia, Firmicutes, and Actinobacteria, and a decrease in Bacteroidetes. These changes epigenetically regulate chronic inflammation, energy metabolism, including glucose and lipid metabolism, and body weight regulation. The traditional Okinawan diet also affects neuroendocrine pathways, particularly the expression of neurotransmitter genes, by increasing serotonin and GABA levels and decreasing cortisol hormone levels.[19]

Table 1. Comparative characteristics of the Traditional Okinawan Diet and Western Dietary pattern

Parameter	Traditional Okinawan Diet	Western Diet
Energy intake[14,15]	Low to moderate energy intake (~1,785 kcal/day); associated with a lean BMI (~21 kg/m ²)	Excess energy intake; associated with a higher prevalence of overweight and obesity
Carbohydrate source	Predominantly complex carbohydrates from sweet potatoes and vegetables; low glycemic load	High intake of refined carbohydrates and added sugars; high glycemic load
Protein intake	Low to moderate protein intake (~9% of total energy), mainly plant-based; includes approximately 85 g/day of soy products (tofu and miso)	Moderate to high protein intake, predominantly animal-based
Fat intake	Low total fat intake; higher proportion of monounsaturated and polyunsaturated fatty acids (MUFA and PUFA); rich in omega-3 fatty acids	High intake of saturated and trans fats
Functional plant foods and dietary fiber[13]	Approximately 30% of energy derived from vegetables; regular consumption of bitter melon (goya), konnyaku, shiitake mushrooms, gobo , hechima , and seaweed, providing soluble fiber (glucomannan) and bioactive compounds	Limited consumption of functional plant foods and dietary fiber
Immunomodulatory food components[12]	Regular intake of shiitake mushrooms (lentinan), hechima (luffin), seaweed, and fermented soy products that support immune regulation and exhibit anticancer potential	Limited intake of natural immunomodulatory foods
Marine-derived bioactive compounds	Frequent seaweed consumption providing iodine, magnesium, folate, fucoxanthin, and astaxanthin with anti-inflammatory and anticancer properties	Minimal intake of marine-derived bioactive compounds
Antioxidant and phytochemical content	High levels of polyphenols, carotenoids, fucoxanthin, anthocyanins, and isoflavones	Relatively low levels of antioxidants and phytochemicals
Salt and sugar intake	Low salt intake (~7 g/day) and minimal added sugar consumption	High salt and added sugar intake
Animal products	Fish consumed approximately three times per week; pork consumed one to two times per week; minimal dairy intake	Frequent consumption of red and processed meats; high dairy intake
Eating behavior and dietary pattern[16]	Practice of Hara Hachi Bu (eating until approximately 80% full); characterized by small portion sizes and mindful eating habits	Large portion sizes and a tendency toward overeating
Functional beverages and fruits[16,17]	Regular consumption of Sanpin-cha tea and Shikuwasa citrus fruit, providing polyphenols and nobiletin with antioxidant effects	Limited consumption of antioxidant-rich beverages and fruits
Alcohol consumption	Low to moderate alcohol intake	Often high or irregular alcohol consumption
Caloric restriction mimetics	Present, including purple sweet potato, turmeric, seaweed, and bitter melon	Generally absent
Dominant molecular effects	Activation of FOXO3 and SIRT1 pathways; enhanced Nrf2 signaling; reduced inflammatory cytokines; improved insulin sensitivity	Increased oxidative stress and inflammation; impaired metabolic signaling pathways
Long-term health outcomes	Lower incidence of cardiovascular disease, cancer, obesity, and type 2 diabetes; associated with increased longevity	Higher prevalence of metabolic syndrome, cardiovascular disease, obesity, and cancer

Okinawan Genetics and Longevity

Besides dietary patterns, lifestyle and environmental factors also play important roles in shaping longevity in Okinawan populations. Recent advances in nutrigenomics emphasize the importance of genetic background and its interaction with long-term dietary exposure. Population-based genetic studies have consistently demonstrated that the FOXO3 gene represents one of the most robust genetic determinates of human longevity. In Okinawan cohorts, carriers of longevity-associated FOXO3 variants exhibit protection against age-related telomere shortening, higher telomerase activity in older adults, better retention of FOXO3 gene expression with age, and more favorable inflammatory profiles, including reduced pro-inflammatory and enhanced anti-inflammatory cytokine levels. These findings provide direct population-level evidence linking FOXO3 genotype to cellular aging markers and healthy aging phenotypes, strengthening the relevance of genetic background in Okinawan longevity.[20]

Importantly, the traditional Okinawan diet may act synergistically with protective genetic variants already present within the population. Lifelong adherence to a nutrient-dense dietary pattern characterized by mild caloric restriction and bioactive food components may enhance the functional impact of longevity-associated alleles, providing a plausible explanation for the high prevalence of healthy aging among Okinawan elders.[14] In parallel, sustained exposure to healthy dietary environments may help preserve genome integrity and attenuate age-related epigenetic drift, as epigenetic regulation including DNA methylation and histone modification is highly responsive to environmental and nutritional inputs. These environmentally driven epigenetic changes may reduce the accumulation of molecular damage during aging and reinforce population level resilience to chronic disease, highlighting an additional layer through which genetic predisposition and lifestyle interact to shape longevity trajectories.[21]

Modern Challenges and Global Relevance

Westernization among the younger generation of Okinawans has brought about major changes in their diet, which was

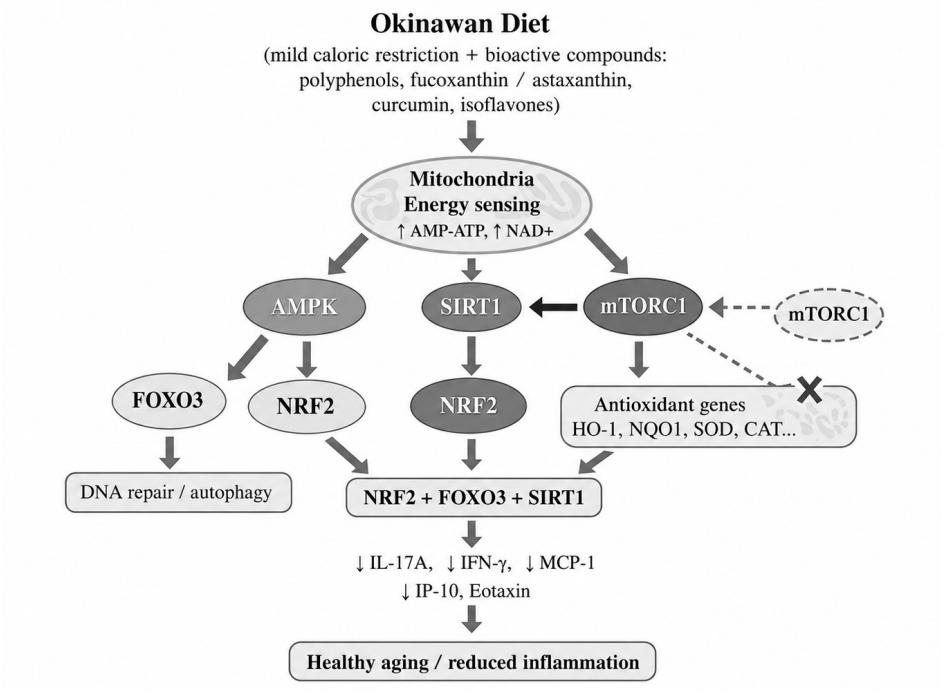

Figure 1. Nutritional pathways involved in Okinawan diet. Bioactive factors and reduced energy intake trigger mitochondria energy-sensing that leads to an increase in the ratio of Adenosine monophosphate (AMP): Adenosine Triphosphate (ATP) and Nicotinamide adenine dinucleotide (NAD+). These actions further stimulate AMPK and SIRT1 activation, leading to the upregulation of FOXO3 and Nrf2 proteins and inhibition of mechanistic Target of Rapamycin Complex (mTORC)1. Activation of these pathways facilitates the induction of antioxidant genes as well as DNA repair mechanisms to result in the suppression of inflammatory cytokines (e.g., IL-17A, IFN-γ).

previously known as one of the healthiest in the world. Over time, the consumption of processed foods, red meat and high sugar drinks has increased, replacing the traditional diet that was low in calories and rich in nutrients.[22] This shift has resulted in a significant increase in the prevalence of obesity, type 2 diabetes mellitus and cardiovascular disease among young Okinawans, that previously rarely experienced these health problems before.[23] This is not only due to changes in the calories and saturated fat consumed, but also due to a decrease in the consumption of fiber, phytochemical, and antioxidants that used to be abundant in their traditional diets and support metabolic health.[22, 24] In addition, a decline in physical activity and the adoption of unhealthy lifestyles have exacerbated the situation. Demographic data shows that the life expectancy advantage previously enjoyed by Okinawans is now declining, especially in the generation born after World War II, who experience higher mortality rates compared to the rest of the Japanese population.[24] This phenomenon demonstrates how modern lifestyle changes can remove the natural protection previously provided by traditional diets and culture.

In addition to impacting physical health, these modern dietary changes also affect the balance of genetic expression that previously supported longevity and metabolic homeostasis.[25] Research shows that the plant-based, low-calorie, anti-inflammatory-rich traditional Okinawan diet support the activation of protective molecular pathways that suppress systemic inflammation and keep metabolism stable.[26, 27] However, these dietary changes that are high in calories, saturated fat and low fiber disrupt protective genetic expression, leading to activation of inflammatory pathways and metabolic dysfunction.[26] In the era of nutrigenomics, it is known that dietary intake affects gene expression through mechanism such as methylation, histone and microRNA regulation, which in turn affects chronic disease risk.[28] In fact, the effect of the interaction between diet and genes can differ between individuals, making a personalized nutrition approach that takes into account an individual's genetic profile and metabolic response important.[29, 30] With the development of technologies such as genetic sequencing, microbiome analysis and the use of big data, we can design more specific dietary interventions, not only to prevent disease but also to optimize individual metabolic health.

The Okinawan phenomenon shows that the world can learn important lessons about the importance of a plant-based, low-calorie and anti-inflammatory diet in supporting long-term health. Adapting the traditional Okinawan diet could serve as a global model to prevent the current surge in chronic diseases.[11] New approaches such as genetically-based personalized nutrition is increasingly relevant to tailor diets to individual genetic profiles, thereby optimizing chronic disease prevention strategies.[30] Adapting the traditional Okinawan diet to Indonesian local preferences can also maintain its health benefits without ignoring the diversity of culinary cultures in different parts of the world. Thus, the traditional Okinawan diet is not just a cultural heritage, but also a globally applicable solution to modern health challenges.

Conclusion

It has been shown by the traditional Okinawan diet that certain food patterns can synergize with epigenetic changes that result in high life expectancy. The interaction between food and genes in the body is studied in nutrigenomics. Studies have shown that Okinawan food can interact with genes involved in aging, such as FOXO3 and SIRT1. Future research must prioritize longitudinal human trials to further distinguish correlative observations from definitive causal nutrigenomic mechanisms and future clinical applications should prioritize the transition from generalized guidelines to precision-based diets. Utilizing genetic testing to identify specific polymorphisms allows for the design of targeted nutritional regimens that proactively mitigate an individual's susceptibility to molecular aging.

Acknowledgement

The author would like to express sincere gratitude to Prodia Education and Research Institute Scholarship who provided encouragement and motivation in the preparation and completion of this review. The author also expresses sincere gratitude to the members of Physiology Class 2023 for their insightful feedback and constructive discussions, which significantly enhanced the clarity and logical progression of this manuscript.

Authors' Contributions

MQ was responsible for the conceptualization of the topic, MQ, AU, and N are responsible for the execution

of the literature search and selection, the synthesis of the findings, and the composition of the manuscript. MQ drafted the manuscript and lastly all authors took parts in giving critical revision of the manuscript.

Conflict of Interest

The authors declare no competing interests.

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