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Probiotics for Preventing Aging and Celecoxib and Berberine for Treating It

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Abstract

Many diseases, such as hypertension, obesity, diabetes, arthritis, and cancer, are caused by inflammation resulting from oxidative stress and dysbiosis. Oxidative stress is triggered by reactive oxygen species (ROS), and long-term inflammation contributes to aging. Inflammation damages DNA, carbohydrates, proteins, and lipids at the cellular and tissue levels. Cytokines such as IL-1β, IL-6, tumor necrosis factor-alpha (TNF-α), and COX-2 are produced through nuclear factor-kappa B (NF-κB) mediation, and ROS is associated with NF-κB activation. Angiogenesis is initiated by the release of angiogenic growth factors and cytokines, including vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), TNF-α, prostaglandin E2 (PGE2), nitric oxide (NO), IL-1, IL-6, and IL-8 from macrophages, affecting endothelial cells. Fibroblasts are activated by TGF-β, which is secreted by macrophages and leads to fibrosis. Prolonged oxidative stress caused by ROS is a major contributor to aging. To delay the aging process, it is important to reduce oxidative stress and NF-κB activation. Celecoxib and symbiosis have the potential to prevent aging by regulating NF-κB activation. Additionally, maintaining a healthy lifestyle with regular exercise and a balanced diet can help reduce oxidative stress and delay aging. It is important to consider a range of anti-aging strategies, including both pharmaceutical interventions and lifestyle changes.

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Introduction

Throughout life, the gut microbiota can predispose individuals to illnesses such as cancer and inflammatory diseases[1]. In a healthy adult human, the gut microbiota is primarily controlled by two phyla: Firmicutes, which includes the genera Faecalibacterium, Lactobacillus, and Roseburia [2]; and Bacteroidetes, which includes the genera Bacteroides and Prevotella. Other active phyla present in smaller amounts include Actinobacteria (primarily Bifidobacterium), Proteobacteria, Verrucomicrobia, Fusobacteria, and Archaea [3] and [4]. These phyla play crucial roles in maintaining gut health by promoting digestion, producing essential vitamins, and regulating the immune system. Imbalances in these phyla can lead to dysbiosis, which is associated with various health conditions. The human gut microbiota is primarily made up of two dominant bacterial phyla in over 90% of cases, and the relative composition remains unchanged by sudden disruptions.

However, this composition is constantly influenced by various environmental factors and can chronically shift towards dysbiosis [5]. Gut Firmicutes, which contain numerous fermenting genes for dietary fibers, may play a role in maintaining the balance of the intestinal mucosa, known as the dietary fiber Firmicutes host axis [2]. Bacteroides species have the potential to cause significant disorders such as bacteremia and abscess formation in any part of the body, with a mortality rate of over 19%. Even though B. fragilis accounts for only 0.5% of the colonic flora, it exhibits strong virulence and antibiotic resistance, similar to other Bacteroides genera [6]. The ability of Bacteroides species to cause severe infections underscores the importance of understanding the composition and dynamics of the gut microbiota. Targeting specific bacterial populations, such as Firmicutes, may provide potential therapeutic strategies for maintaining gut health and preventing dysbiosis-related diseases.

Normal intestinal homeostasis, as indicated by a balanced Firmicutes/Bacteroidetes (F/B) ratio, is essential for overall health. Dysbiosis, characterized by an imbalance between Firmicutes and Bacteroidetes, is associated with inflammatory bowel disease (IBD) when the F/B ratio is lower, and with obesity when the F/B ratio is higher. The genus Lactobacillus has been found to be effective in maintaining the F/B ratio and in the treatment of obesity and IBD [7]. Fusobacterium nucleatum, a pathogenic bacterium, thrives in the rectosigmoid colon and is associated with periodontitis, and inflammatory diseases [8] and [9]. In Alzheimer's disease, F. nucleatum has been found to induce morphological changes and increase the expression of proinflammatory cytokines, such as TNF-α and IL-1β, in microglial cells [8]. Additionally, the presence of F. nucleatum has been linked to a higher risk of colorectal cancer due to its ability to promote inflammation and inhibit the immune response [10]. Therefore, targeting F. nucleatum with probiotics containing Lactobacillus may help reduce the risk of various inflammatory diseases and conditions.

Dysbiosis can lead to diseases of the gastrointestinal tract, the immune system, and the central nervous system (gut-brain axis) [5]. The gut microbiota is pathophysiologically related to aging at all stages of life[10]. Certain bacteria activate specific metabolic pathways in the human diet, which in turn stimulates human metabolism [11]. Enzymes in the gastrointestinal tract, particularly the colon, perform denitrification, fermentation, hydrolysis, and other processes that human enzymes cannot perform. They also aid in the metabolism of dietary proteins, carbohydrates, bile acids, and vitamins [9] and [11]. Additionally, the gut microbiota plays a crucial role in regulating the immune system and modulating inflammation [10]. The intricate relationship between gut microbiota and human health emphasizes the importance of maintaining a diverse and balanced microbial community in the gastrointestinal tract.

There are two main categories of dietary carbohydrates: digestible and non-digestible. Digestible carbohydrates include starches, monosaccharides, and disaccharides. Short-chain fatty acids (SCFAs) are beneficial compounds produced by the gut microbiota during the fermentation of soluble fibers, which are non-digestible [12]. The interaction between gut bacteria and dietary proteins is crucial for the host's immune response. The gut microbiota metabolizes proteins to produce amino acids, which are linked to human health and disease. The USDA's Dietary Guidelines recommend consuming 10-35% of calories from protein, 45-65% from carbs, and 20-35% from fat to achieve an appropriate ratio between protein, carbs, and fat [13]. A balanced diet with adequate protein intake is essential for overall health and well-being. Considering the source and quality of protein is important to optimize its benefits for the gut microbiota and immune system.

Polyphenols are a diverse group of chemical compounds, most of which are l-phenylalanines containing more than two phenolic groups. Stilbenes, lignans, flavonoids, and coumarins are all considered polyphenols, and polymerized polyphenols include lignins and tannins [14]. The tannins and soluble polyphenols found in persimmon (Diospyros kaki) effectively deactivate the COVID-19 virus in saliva by binding strongly to proteins [15]. Oxidative stress, which occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify them [16], can lead to persistent inflammation. ROS include singlet oxygen ($^1O_2$), hydroxyl radicals ($OH^\bullet$), hydrogen peroxide (H_2O_2), and superoxide radicals ($O_2^{\bullet-}$), and can be produced by both external sources such as heavy metals, cigarette smoke, alcohol, and radiation, as well as internal sources like microorganisms [17]. These free radicals can cause damage to cellular components, leading to various diseases, including cancer and neurodegenerative disorders. Therefore, it is important to maintain a balance between ROS production and elimination for overall health and well-being.

Aging is caused by endogenous free radicals [16], which are controlled by proinflammatory cytokines generated by tumor necrosis factor-alpha (TNF-α) and nuclear factor-kappa B (NF-κB)/activator protein 1 (AP-1) activation[18]. Metabolic abnormalities exacerbate chronic inflammation, and bile acids play a role in boosting systemic immunometabolism [19]. Age-related pathophysiological conditions such as diabetes, Parkinson's disease, Alzheimer's disease, and stroke are linked to metabolic inflammation. Chronic inflammation, facilitated by the interaction of gut microbiota with dysregulated bile acids, contributes to aging and can also lead to the development of cardiovascular diseases and certain types of cancer [20]. Understanding the role of metabolic inflammation in these age-related diseases is crucial for developing targeted therapeutic interventions.

Studies have shown that consuming nine vitamins with high antioxidant properties can lower the risk of chronic diseases. Low intake of these vitamins increases the risk of aging [21]. Vitamin A is derived from carotenoids, which are tetraterpene pigments and precursors of vitamin A. There are over 850 different carotenoids, and they function as antioxidants and boost the immune system [22]. Carotenoids are converted to retinoids (retinol, retinal, and retinoic acid) through vitamin A. Preformed vitamin A is only found in animal products such as meat, fish, and milk. Retinoids have various biological functions, including promoting cellular growth, modulating the immune system, and exhibiting anti-tumor activities. Retinol has been found to have a strong ability to slow down the aging process [21] and [23].

As people age, their ability to metabolize vitamin D into active vitamin D (calcitriol) decreases by 50% due to declining renal function. This reduced metabolism can result in lower calcium absorption and potential bone health issues. Therefore, older adults should consider supplementation or increased sun exposure to maintain sufficient levels of vitamin D. This reduction in calcitriol production results in decreased calcium absorption 10 to 15 years before calcitriol is produced [24]. In Japan, the maximum tolerated consumption for men and women over the age of 18 is set at 100 mcg (40 IU), while the recommended daily intake for both genders is 8.5 mcg (40 IU). Vitamin D regulates the physiological processes of every organ and the metabolism of calcium and bone through the cellular catabolic process known as autophagy, which breaks down malfunctioning organelles and cytoplasmic components to produce nutrition and maintain homeostasis [25]. Calcitriol, the active form of vitamin D, plays a crucial role in regulating calcium levels in the body by promoting calcium absorption in the intestines and maintaining proper levels of calcium and phosphorus in the blood. Vitamin E is a potent antioxidant with eight derivatives. Vitamin E deficiency is rarely observed in conditions such as short bowel syndrome, abetalipoproteinemia, cystic fibrosis, chronic cholestatic liver disease, and other unusual conditions [21]. Tomatoes contain beneficial components including vitamin C, vitamin E, and other carotenoids, with lycopene being the main carotenoid [26]. High intake of lycopene and vitamin E can prevent the development and slow the progression of prostate cancer [22] and [27]. Research suggests that telomere length (TL) is a highly accurate indicator of aging[28]. Both vitamin C and vitamin E have antioxidant properties, and increasing dietary intake of vitamin E may help maintain telomere length [29]. Furthermore, studies have shown that vitamin E supplementation can protect against telomere shortening, supporting its role in promoting overall health and longevity. Therefore, including foods rich in both vitamin C and vitamin E, such as tomatoes, into the diet may be beneficial for promoting healthy aging. Vitamin C has antioxidant qualities that shield cells from oxidative stress and extend their lives [30]. Antioxidants like vitamin C and E in the cell and the interstitial fluids neutralize ROS [31]. Consuming a diet rich in fruits and vegetables can help increase antioxidant levels in the body, promoting overall health and longevity. Including a variety of colorful produce in your meals can ensure you're getting a wide range of beneficial antioxidants.

Vitamin B1, also known as thiamine, is one of the eight B vitamins. It acts as a cofactor for enzymes such as transketolase, a-ketoglutarate dehydrogenase, and pyruvate dehydrogenase when in the form of thiamine pyrophosphate. Thiamine deficiency can lead to disorders like beriberi and is associated with symptoms that affect the neurological, cardiac, and gastrointestinal systems, accelerating aging. The recommended daily dose for individuals over the age of eighteen, is 1.1-1.2 mg/day. Consuming a balanced diet that includes thiamine-rich foods such as whole grains, legumes, nuts, and pork is important for preventing deficiency. Excessive levels of serum B1 can lead to increased ATP synthesis,

which can deplete glutathione, cause lipid peroxidation, and release free radicals containing oleic acid. Severe thiamine deficiency can result in Wernicke-Korsakoff syndrome, characterized by mental confusion, memory issues, and eye movement abnormalities.

Riboflavin, also known as vitamin B2, is primarily utilized in the production of coenzymes such as flavin mononucleotide and flavin adenine dinucleotide, which are essential for the metabolism of proteins, fats, and carbohydrates. Riboflavin also plays a role in regulating endocrine disorders that affect human metabolism and energy generation, such as insufficient thyroid hormone and aldosterone [32]. Vitamin B6, on the other hand, is a coenzyme involved in over 150 metabolic activities necessary for the metabolism of lipids, amino acids, carbohydrates, and nucleic acids. A deficiency in antioxidant vitamin B6 has been linked to various illnesses, including cancer, heart disease, and diabetes [33]. Additionally, vitamin B6 is crucial for the synthesis of neurotransmitters such as serotonin and dopamine, which are involved in mood regulation and cognitive function. Furthermore, vitamin B6 is essential for the production of hemoglobin, which is necessary for oxygen transport in the blood.

People's bodies become less capable of absorbing vitamin B12 as they get older. Low intake of vitamin B12 can lead to pernicious anemia in aging individuals, as well as an imbalance of stomach acids and enzymes in atrophic gastritis, which are the two main causes of vitamin B12 deficiency [34]. Symptoms of B12 deficiency include anemia, digestive issues, and neurodegenerative symptoms, ranging from mild to severe spinal cord disruptions [35]. High serum B12 levels can interfere with K levels during hematopoiesis, leading to stomach problems and respiratory difficulties. It is important for individuals, especially older adults, to monitor their vitamin B12 levels and consider supplementation if necessary. Consulting with a healthcare provider can help determine the appropriate dosage and prevent potential complications associated with B12 deficiency.

Materials and Methods

A literature review was carried out across multiple reputable databases pertaining to computers, aging, cytokines, celecoxib, NF-κB, vitamins, ROS, inflammation, probiotics, berberine, Phellodendron amurense. The essential elements of this article were located using these keywords. We used data from the Statista 2024 website to compile age group statistics for the six countries from 2012 to 2022. Across all databases, 204 articles could be located. We quickly skimmed each article's title and summary to pick out important technical details. This has led to a clear explanation of these features using a substantial scientific technique, which has improved the article's scientific content. The National Institute of Health (64), Europe PMC (4), Frontiers (4), ResearchGate (4), ScienceDirect (3), Google Scholar (3), Elsevier (2), Springer (1), PubMed (1), Nature (1), and BMC microbiology (1), were the sources of the pertinent papers.

Results and Discussion

To emphasize the importance of this research in addressing health issues for elderly individuals and to assist countries worldwide in developing effective solutions, we analyzed the age demographics of six countries (Japan, Egypt, France,

the United States, Brazil, and Australia) representing six continents. This analysis will help us determine the proportion of elderly individuals in these societies who can actively participate in addressing global challenges. Policymakers and healthcare providers will benefit from this data to tailor their strategies to meet the specific needs of aging populations in diverse regions. By understanding the age distribution of the population, we can optimize healthcare to improve the well-being of elderly individuals globally. In the last decade, Japan has experienced a significant increase in its aging population (Figure 1). By 2022, over 25% of Japanese residents will be 65 years old or older. This demographic shift is primarily due to higher life expectancy and declining birth rates. The aging population poses challenges to Japan's healthcare system and economy, necessitating innovative solutions to cater to the needs of the elderly.

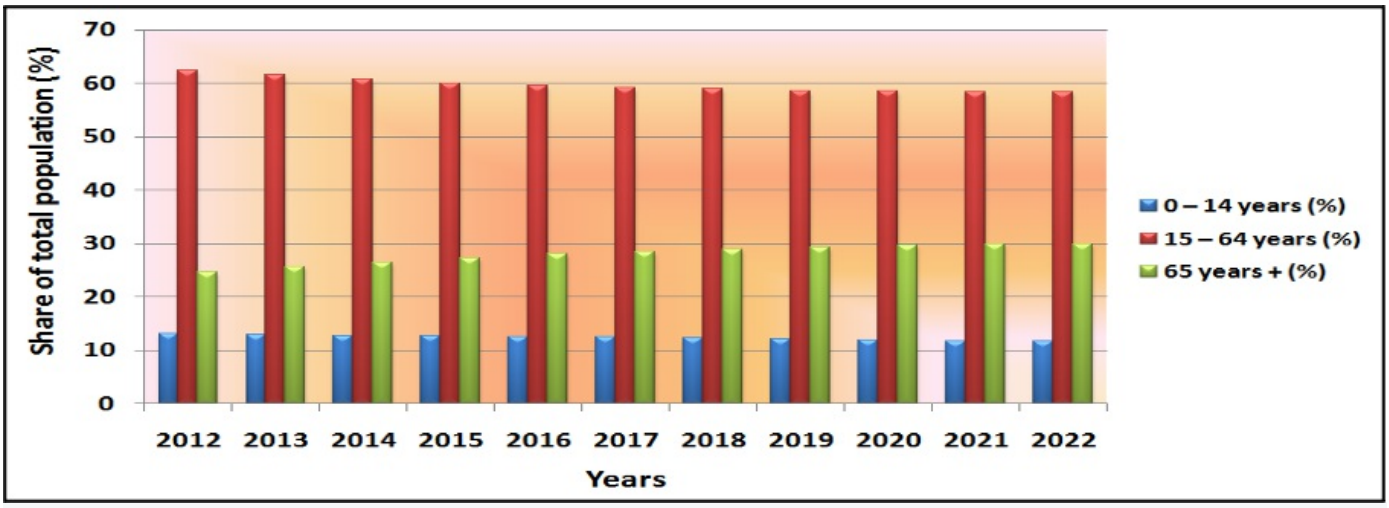

Figure 1. Age structure from 2012 to 2022 in Japan.

In 2022, individuals aged 0 to 14 made up 32.86% of Egypt's population (Figure 2). The working-age group, spanning from 15 to 64 years old, accounted for approximately 62.31% of the total population. However, this age group's share has been gradually decreasing, dropping from 62.61% in 2011 to 62.17% in 2021. This trend suggests a potential shift in Egypt's demographic composition in the future, which could have implications for various sectors such as healthcare, education, and labor force participation. The low percentage of elderly individuals in Egyptian society underscores the pressing need for healthcare services and the importance of finding timely and acceptable solutions for this demographic. As the population ages, there will be an increased demand for specialized medical facilities and services tailored to meet the unique needs of the elderly. Healthcare infrastructure and initiatives targeting this population must receive top priority from authorities.

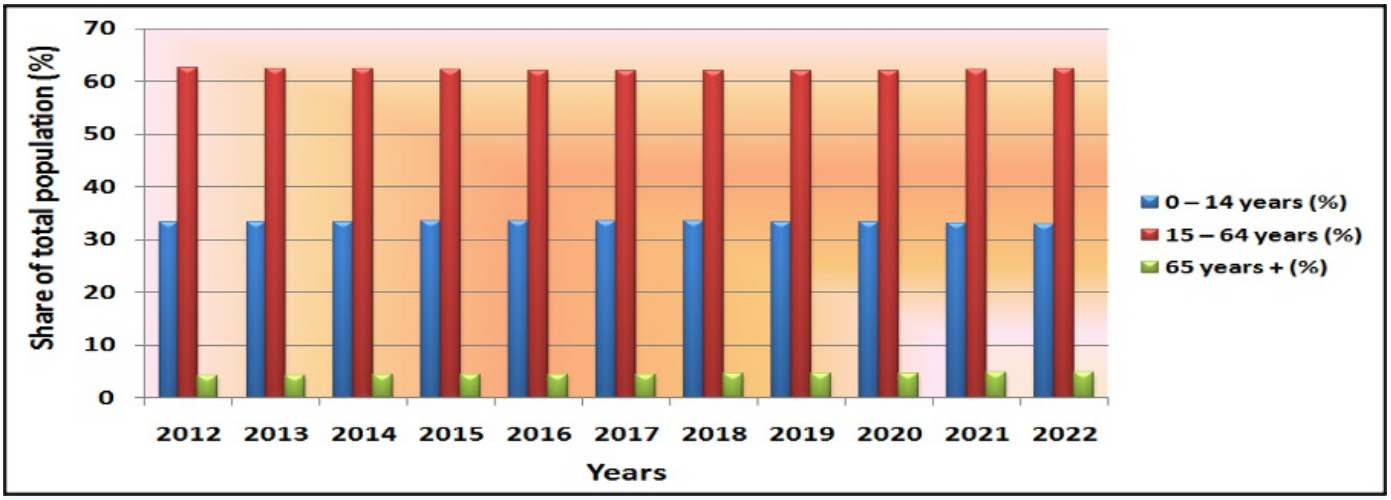

Figure 2. Age structure from 2012 to 2022 in Egypt.

The age distribution of French citizens from 2012 to 2022 is depicted in this statistic (Figure 3). In 2022, 17.2% of French people were under 14 years old, 61.14% were aged 15 to 64, and 21.66% were over 65. The data shows a gradual aging of France's population, with a decrease in the younger age group and an increase in the older age group. This demographic shift may have implications for the nation's social services, healthcare, and pension systems.

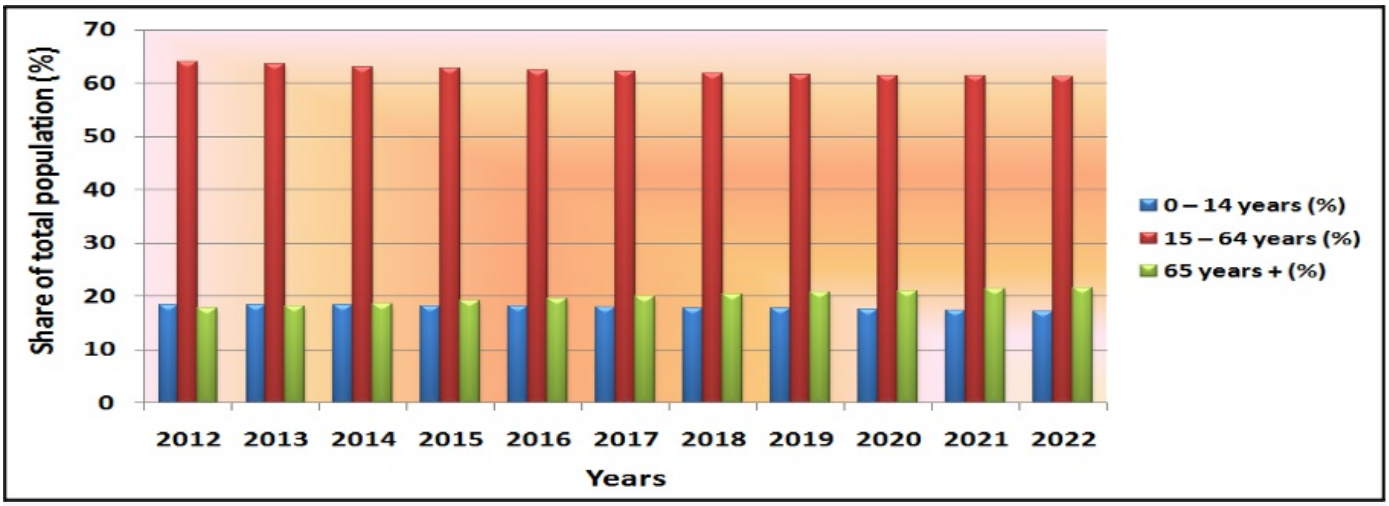

Figure 3. Age structure from 2012 to 2022 in France.

The age distribution in the US from 2012 to 2022 is depicted in this statistic (Figure 4). In 2022, approximately 17.96% of Americans were aged 0-14, 64.91 percent were aged 15-64, and 17.13% were over 65. The distribution of the working-age population and the younger and older populations is relatively balanced based on the data. The ongoing trend of an aging population is expected to persist, potentially posing challenges for the social security and healthcare systems in the future.

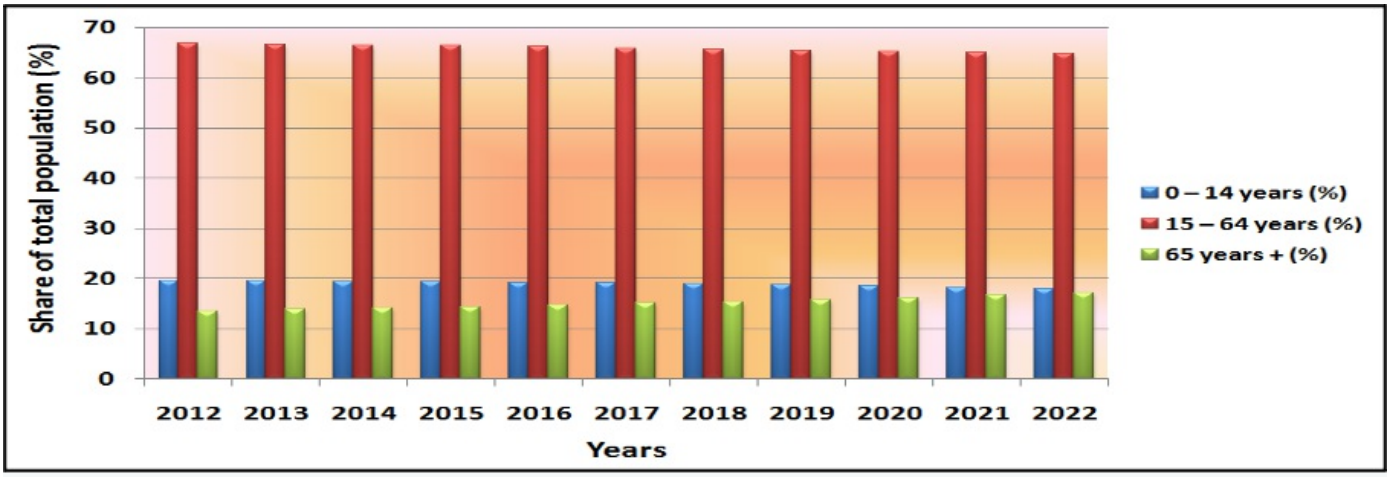

Figure 4. Age structure from 2012 to 2022 in the US.

This statistic illustrates the age distribution in Brazil from 2012 to 2022 (Figure 5). In 2022, around 20.27% of Brazil's population was aged 0 to 14, indicating a significant proportion of young individuals in the country. Policymakers need to consider the educational, healthcare, and social service needs and opportunities for elderly individuals.

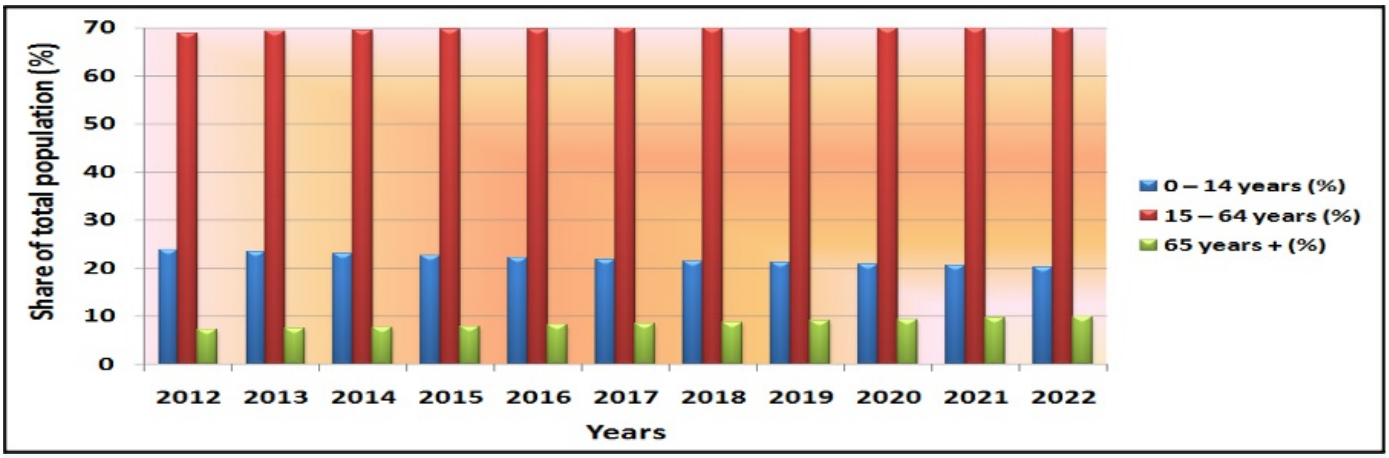

Figure 5. Age structure from 2012 to 2022 in Brazil.

In Australia, the age distribution of individuals over 65 and those aged 0-14 is very similar, indicating a potentially high birth rate or longer life expectancy in the population (Figure 6). This similarity may have future implications for social services and healthcare. The largest age group in the population falls between 15 and 64 years old. The average age of the population has been increasing gradually due to lower fertility rates and longer life expectancies. To encourage elderly individuals to participate in the Australian community, it is essential to provide them with healthcare services.

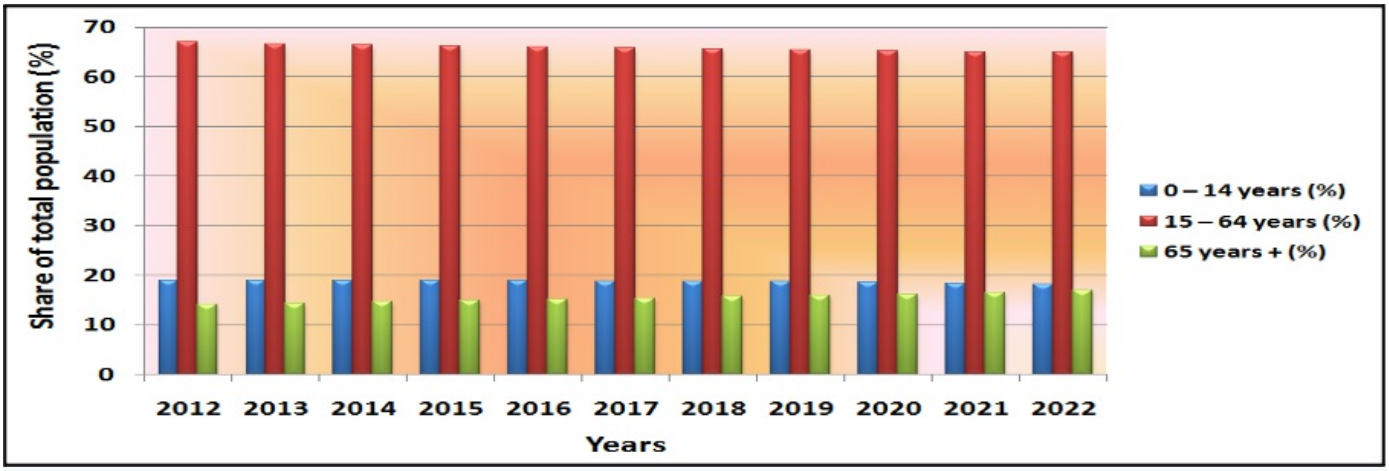

Figure 6. Age structure from 2012 to 2022 in Australia.

Numerous environmental factors, including geography, socioeconomic status, religion, health, sociocultural milieu, and dietary habits, have an impact on the gut microbiota of these countries. These elements influence an individual's general health as well as their susceptibility to certain disorders. Comprehending these variations in diet and medical care can assist researchers in creating focused treatments to enhance general health. For example, individuals in countries with a diet high in fiber and fermented foods tend to have a more diverse gut microbiota, which is associated with better overall health. Additionally, understanding how these factors interact can lead to personalized interventions that target specific populations for improved health outcomes.

The gut microbiota is linked to a range of human health issues, including inflammatory bowel disease (IBD), metabolic diseases (such as diabetes, and obesity), allergies, cardiometabolic diseases, and neurodegenerative diseases [36] and [37]. Short-chain fatty acids (SCFAs) produced by gut microbiota, such as Bifidobacterium, Faecalibacterium, and Bacteroides, promote the production of neutrophils, basophils, eosinophils, and lymphocytes [37]. However, the production of SCFAs declines with age, particularly in the age range of 66 to 80 years old [38]. SCFAs are produced through the fermentation of dietary fibers, and resistant starch by gut bacteria in the colon [39]. These SCFAs are essential for maintaining gut health and have been linked to various age-related diseases. Therefore, dietary interventions that promote a healthy gut microbiota may help prevent or manage these conditions in older adults. A decrease in mitochondrial metabolism, which is considered the main source of cellular energy production, is a key characteristic of aging. Mitochondria are closely linked to the control of aging and lifespan through energy metabolism [40]. The primary components of SCFAs are the small organic monocarboxylic acids butyrate (C4), propionate (C3), and acetate (C2), which are produced at a daily rate of approximately 60:20:20 molars [39]. SCFAs play a vital role in maintaining gut health and have been found to possess anti-inflammatory and anti-cancer properties. Furthermore, they are known to regulate energy balance and metabolism in the body.

The silent information regulator, also known as SIRT, consists of two proteins that are indicative of SIRT1-7-dependent nicotinamide adenine dinucleotide (NAD^+) deacetylases [41]. Acetate can be used to convert fatty acids, glucose, and amino acids into acetyl-CoA. Acetyl-CoA is produced in the mitochondria from acetate by acetyl-CoA synthetase

(AceCS2), and it is deacetylated by SIRT3. Acetyl-CoA has numerous anabolic uses [40]. Sirtuins, as members of the class III histone deacetylase family, deacetylate transcription factors such as NF-κB, in addition to histones. Most SIRTs inhibit NF-κB activity, while activated NF-κB accelerates aging [42] and [43]. Therefore, SIRT3's role in regulating acetate metabolism and deacetylating transcription factors like NF-κB has implications for aging and longevity [40] and [44]. By inhibiting NF-κB activity, SIRT3 may help slow down the aging process and promote longevity in humans.

Elevated propionate levels can lead to a range of health issues. Deficiency in the propionyl-CoA carboxylase enzyme can result in propionic acidemia, which manifests as asymptomatic cardiomyopathy, metabolic acidosis, and central nervous system damage [45] and [46]. The main objective in reducing propionate levels is to achieve a healthy balance of gut bacteria, known as synbiosis. Vitamin B12 plays a role in breaking down propionate. An increase in the F/B ratio of bacteria can promote propionate production. However, a decrease in propionate is often linked to a rise in butyrate levels as well [45]. In individuals with dysbiosis, particularly middle-aged or older people who are prediabetic, there is a tendency to produce less butyrate [47]. This reduction in butyrate production can disrupt the balance of gut microbiota, leading to various health problems. Therefore, dietary interventions aimed at promoting a healthy balance of propionate and butyrate may be beneficial for individuals at risk of propionic acidemia.

Histone acetyltransferases (HATs) and histone deacetylases (HDACs) primarily operate in neurons, microglia, and astrocytes to regulate essential cellular processes such as cell cycle arrest, differentiation, and apoptosis [48] and [49]. Butyrate, acting as an HDAC inhibitor, utilizes the same mechanisms and is currently undergoing clinical trials as a safe anti-neoplastic treatment [49]. Furthermore, butyrate has demonstrated anti-inflammatory effects by inhibiting the activation of nuclear factor kappa B (NF-κB) and reducing the production of pro-inflammatory cytokines. This dual mode of action positions butyrate as a promising therapeutic agent for various diseases characterized by dysregulated inflammation and cell proliferation.

Adaptive immunity responds to antigenic stimuli through T cell and B cell dysfunction. The activity of antigen receptor genes produced by these cells and the changing number and ratio of lymphocyte subpopulations leads to alterations [50]. The skin serves as a barrier against various infections, including radiation, which can lead to conditions such as psoriasis and cancer. These skin conditions can significantly impact patients' quality of life and accelerate the aging process. Flavonoids, with their antioxidant and anti-inflammatory properties, have been found to regulate changes in cells and the biochemical system [51]. They show potential benefits in managing skin conditions like psoriasis and cancer, as well as in improving patients' quality of life and slowing down the aging process.

Propolis, collected by honey bees, consists mainly of resin (50-70%), oil and wax (30-50%), and pollen (5-10%). It can be used to make paste antibiotics or as building materials. Propolis contains over 240 compounds, including antioxidants and anti-inflammatory agents, which have been shown to have anti-aging properties and to help prevent diseases such as diabetes, cancer, Alzheimer's, Parkinson's, and arthritis [52] and [53]. It also contains a significant amount of flavonoids, organic compounds with phenolic structures found in various plants, including fruits, vegetables, cereals, flowers, tea, and wine [54]. Flavonoids have been studied for their potential health benefits, such as reducing the risk of chronic diseases and improving overall health. Moreover, propolis has been used for centuries in traditional medicine fordue to its

antimicrobial and anti-inflammatory properties.

Cruciferous plants, also known as the Brassicaceae family, naturally contain glucosinolates, which are the precursors of isothiocyanates. These isothiocyanates are produced when the glucosinolates are enzymatically hydrolyzed by the myrosinase system [55]. Sulforaphane, a potent isothiocyanate, activates antioxidant enzymes through the transcription factor Nrf2, providing protection against ROS, lipopolysaccharides (LPS), and reactive nitrogen species (RNS) [56]. These enzymes are essential for the body's defense against oxidative stress and inflammation, making cruciferous vegetables an important part of a healthy diet. Studies have also suggested that sulforaphane may have potential anti-cancer properties by inhibiting tumor growth and inducing apoptosis in cancer cells [57].

The World Health Organization (WHO) lists several common conditions associated with aging, including hearing loss, cataracts, refractive errors, back and neck pain, osteoarthritis, chronic obstructive pulmonary disease, diabetes, depression, and dementia. As people age, they are more likely to experience multiple conditions simultaneously [58]. Additionally, cerebrovascular diseases such as strokes and dementia contribute to death and disability in the elderly, with risk factors including hypertension, diabetes, carotid artery stenosis, atrial fibrillation, hyperlipidemia, and smoking [59].

With respect to heart disease and hypertension, it appears that atherogenic stimuli, such as high cholesterol, can trigger an inflammatory response by activating mechanisms that recruit monocyte-derived leukocytes. Atherosclerosis is caused by hypertension and inflammation. Similarly, hyperlipidemia can increase the inflammatory response by inducing macrophage expression. These pathways lead to oxidative stress on the artery wall, resulting in atherosclerosis and hypertension [60]. In summary, the combination of high cholesterol, hypertension, and inflammation can lead to severe cardiovascular complications. It is crucial to manage these risk factors through lifestyle changes and medication to prevent the development of heart disease.

Cancer is the second leading cause of death globally, responsible for 50% of deaths in people over 70 and 40% in the 50-70 age group. Aging and cancer share many common processes, including the activation of proinflammatory factors such as IL-1β, IL-6, and TNF-α through NF-κB [61]. These factors play a key role in promoting chronic inflammation, which can contribute to the onset and advancement of cancer. Exploring the connection between aging, inflammation, and cancer could lead to new approaches for prevention and treatment.

Oxidative stress damages articular and non-articular cells, leading to persistent inflammation in osteoarthritis. Elderly individuals experience cellular damage and chronic inflammatory reactions. Chondrocyte mortality is associated with mitochondrial dysfunction caused by DNA damage [62] and [63], mediated by inflammatory cytokines such as TNF-α and IL-1β. This process contributes to the development of osteoarthritis, a degenerative joint disease that affects millions of people worldwide. Osteoarthritis is characterized by the breakdown of cartilage in the joints, resulting in pain, stiffness, and reduced mobility.

Osteoporosis is the natural loss of bone density that occurs with aging. It is maintained through a balance between osteoblasts, which build new bone, and osteoclasts, which break down existing bone. Osteoclast differentiation is influenced by factors such as parathyroid hormone (PTH), 1,25-vitamin D3, and proinflammatory cytokines like IL-1β, IL-6,

IL-11, and TNF-α. In women, the decrease in estrogen levels as they age is a major factor in the development of osteoporosis [64]. This decline in estrogen leads to increased osteoclast activity, resulting in a gradual loss of bone density over time. Hormone replacement therapy can help counteract this effect and reduce the risk of osteoporosis in postmenopausal women.

Insulin-dependent diabetes (Type 2) is a major health concern for the elderly. Lower than 6.5% HbA1c values are advised. Proinflammatory cytokines from diabetes itself cause oxidative stress, DNA damage, and systemic chronic inflammation, which in turn cause a host of other disorders [65]. Diabetes can also lead to complications such as heart disease, kidney failure, and nerve damage. It is important for elderly individuals with diabetes to closely monitor their blood sugar levels and follow a healthy lifestyle to prevent further health issues.

Parkinson's disease is a neurocognitive illness that combines Lewy body dementia with Parkinson's disease. Both conditions share physical characteristics in the cortex and subcortex, including tau, β-amyloid, and α-synuclein/Lewy body [66]. According to the National Institute on Aging, the number of people with dementia, including Alzheimer's disease), doubles approximately every five years after the age of 65, and about one-third of adults over 85 may have Alzheimer's [67]. Alzheimer's disease is currently considered incurable and is caused by neurodegeneration and neuroinflammation [68]. However, synbiosis and anti-inflammatory medications may help to halt or prevent its progression. Lifestyle changes such as regular exercise, a healthy diet, and mental stimulation have also been shown to potentially reduce the risk of developing Alzheimer's disease. Early detection and intervention are crucial for managing the disease's progression and improving the quality of life for those affected.

Chronic obstructive pulmonary disease (COPD) is a condition characterized by inflammation of the pulmonary tissues, including the pulmonary vasculature, lung parenchyma, and airways. This inflammation is associated with the activation of neutrophils and macrophages, which release immunological mediators such as IL-1β, IL-6, and TNF-α in response to environmental stressors. These mediators lead to oxidative stress and emphysema [69]. The chronic inflammatory response in the lungs causes airflow limitation and difficulty breathing, which are typical symptoms of COPD. Smoking is the primary risk factor for developing COPD due to the harmful effects of tobacco smoke on lung tissue.

Oxidative stress can cause damage to the lens, leading to age-related cataracts. Various clinical conditions, such as diabetes, obesity, smoking, and UV radiation, are known to be triggered by oxidative stress [70]. It is important to include antioxidant-rich foods in your diet to combat oxidative stress and reduce the risk of developing age-related cataracts. Maintaining a healthy lifestyle with regular exercise and proper nutrition can also help prevent conditions related to oxidative stress. Regular exercise and a balanced diet can improve overall health and reduce the risk of age-related cataracts. Additionally, wearing sunglasses outdoors to protect your eyes from excessive UV exposure can also help prevent oxidative stress-related damage to the lens.

Age-related macular degeneration (AMD) is a condition that affects the macula, which is the central part of the retina. Seniors in their 50s and 60s who have AMD often experience difficulty with routine tasks such as reading. Factors such as menstruation, high blood pressure, heredity, and sun exposure can lead to burst blood vessels in the macula, causing

irreversible damage [71].

Treating the signs of aging and preventing the signs of aging in older adults are the two approaches to managing the effects of aging. Both approaches can be effective in maintaining a youthful appearance and promoting overall health and well-being. They are listed in the following order: treatment and prevention of aging.

- **Treatment**

By focusing on important pathways involved in the development of cancer and inflammatory illnesses, celecoxib has the potential to prevent these conditions as well as treat them. Celecoxib has the potential to prevent and treat cancer and inflammatory illnesses by targeting key pathways involved in their development. Its dual mode of action makes it a valuable option for effectively managing these conditions. Celecoxib acts as an effective treatment for inflammatory diseases and cancer by promoting apoptosis and inhibiting angiogenesis. Called a diaryl-substituted pyrazole, celecoxib is also known by its chemical designation, 4-[5-(4-methylphenyl)- 3- (trifluoromethyl) -1H- pyrazol-1-yl] benzenesulfonamide. It is a nonsteroidal anti-inflammatory drug (NSAID) that works by inhibiting the enzyme cyclooxygenase-2 (COX-2). Celecoxib also suppresses the activation of NF-κB, which reduces the production of inflammatory cytokines [72]. Celecoxib is commonly used to treat pain, inflammation, and swelling caused by conditions such as arthritis. Celebrexin's analgesic, anti-inflammatory, and antipyretic properties are a result of this pharmacologic activity. Celecoxib may have a less negative impact on platelet function than aspirin because it mildly inhibits COX-1. This makes it a preferred option for patients who need pain relief without affecting their platelet function.

However, like other NSAIDs, celecoxib may still carry risks of gastrointestinal bleeding and cardiovascular events. As will be covered in more detail below, celecoxib also possesses anticancer qualities. These abilities are exerted by binding cadherin-11 (CDH11), which is probably important for the malignant development of cancerous cells. In addition to its pain-relieving properties, celecoxib has been studied for its potential in cancer treatment due to its ability to bind CDH11. This mechanism may play a role in inhibiting the growth and spread of cancer cells. Since cytochrome P450 2C9 (CYP2C9) is involved in the extensive metabolism of celecoxib, it is possible that it will interact with other drugs that are CYP2C9 substrates. [73]. Therefore, caution should be taken when combining celecoxib with other medications that are metabolized by CYP2C9 to avoid potential drug interactions. Celecoxib is available in four different dosages: 50, 100, 200, and 400 mg, and is administered orally. In certain cases, celecoxib can be incorporated into specially prepared compounds for topical application, with or without the use of iontophoresis or other topical delivery methods.

The recommended dosages for various conditions are as follows: Osteoarthritis: 200 mg orally once daily or 100 mg twice daily. Rheumatoid arthritis: 100-200 mg orally twice daily, using the lowest effective dose. Ankylosing spondylitis: 200 mg orally once daily, with a maximum dosage of 400 mg. Dysmenorrhea: 200 mg orally twice daily, with a maximum dosage of 400 mg. Acute pain: 200 mg orally twice daily, with the option to start with a 400 mg single dose on the first day and adjust as needed. All doses should be taken with food if gastrointestinal discomfort occurs. For patients with inadequate CYP2C9 metabolism, start with 50% of the lowest dose. Avoid use in patients with a creatinine clearance less than 30 mL/s due to renal impairment or in cases of hepatic insufficiency in children in Pugh Class C. If there is no improvement

after six weeks at the maximum dose, consider discontinuing the medication. It is important for healthcare providers to consider these factors when prescribing celecoxib to patients, especially those with cancer who may be taking multiple medications.

The Japanese herb *Phellodendron amurense*, known as KIHADA in Japanese, is a rich source of berberine, an isoquinoline alkaloid used to treat microbial diarrhea. Berberine has diverse biological and pharmacological properties, making it effective in treating conditions such as fibromyalgia (FM) and cancer. Berberine inhibits pro-inflammatory and pro-angiogenic molecules through its anti-angiogenic activity [74], by activating AMP-activated protein kinase (AMPK) and suppressing NF-κB/AP-1. This results in the down-regulation of cytokine expression, including TNF-α, IL-1β, IL-6, MCP-1, iNOS, and COX-2 [75] and [76]. Additionally, berberine has demonstrated anti-cancer effects by inducing apoptosis in cancer cells and inhibiting tumor growth.

In the US, lung cancer is the leading cause of cancer-related deaths for both men and women. Most cases are diagnosed at an advanced stage, resulting in a high mortality rate of over 90% and a 5-year survival rate of only 16%, despite recent advancements [77]. Recent research has demonstrated that the bark extract of *Phellodendron amurense* (P. amurense) can inhibit the proliferation of prostate cancer cells by blocking Akt/CREB -mediated cyclin D1 activation. Additionally, it has been shown to prevent the development of prostate cancer [78]. Cox-2 activation mediated by CREB was reduced by P. amurense extract [79]. The extract also reduces Cox-2 activation mediated by CREB, a signaling pathway associated with lung and prostate cancer [80] and [81]. These findings suggest that P. amurense bark extract may have potential therapeutic benefits in preventing and treating various types of cancer, not limited to prostate cancer.

Screening programs and treatment innovations offer hope for better outcomes, but quitting smoking is essential for lowering the risk of developing this deadly disease. These findings highlight berberine as a promising natural compound for treating various diseases. Superoxide anion radical ($O_2^{\bullet-}$) is neutralized by superoxide dismutase (SOD) and catalase (CAT) to form H_2O and O_2, reducing the harmful H_2O_2 levels. Berberine shows promise in enhancing SOD and CAT activity, leading to a reduction in ROS, particularly H_2O_2. This can significantly alleviate oxidative stress [82]. Berberine has limited bioavailability due to its poor water solubility and intestinal absorption [83] and [84]. However, oral administration has proven effective in treating various conditions, such as diabetes mellitus. Berberine is metabolized by gut microbiota into dihydroberberine (dhBBR), which is five times more absorbable. Upon absorption, dhBBR undergoes an unstable oxidation process, reverting back to berberine [84]. This transformation enhances berberine's bioavailability and therapeutic efficacy. Therefore, oral administration of berberine may offer a more efficient treatment approach for oxidative stress-related conditions. Further research is necessary to fully understand its anti-cancer properties and mechanisms of action.

- **Prevention of aging**

Probiotics play a crucial role in maintaining gut health in the elderly by promoting the growth of beneficial microorganisms like Firmicutes and Actinobacteria (Lactophilus and Bifidobacteria) while reducing pathogenic taxa in the Proteobacteria phylum, such as Salmonella and Escherichia coli [85]. Supplements and meals fermented by good bacteria are good sources of probiotics. Sauerkraut, which is finely chopped raw cabbage that has been fermented by lactic acid bacteria,

yogurt, kefir, and kimchi are examples of fermented foods [86], [87], and [88]. The term "fermented foods" refers to meals or drinks that are produced through the enzymatic conversion of food ingredients and controlled microbial growth. These foods are formed by controlled microbial growth and enzymatic action, which results in unique flavors and textures. Figure (7) shows the two strategies for managing the consequences of aging in older people are treating the signs of aging and preventing the signs of aging.

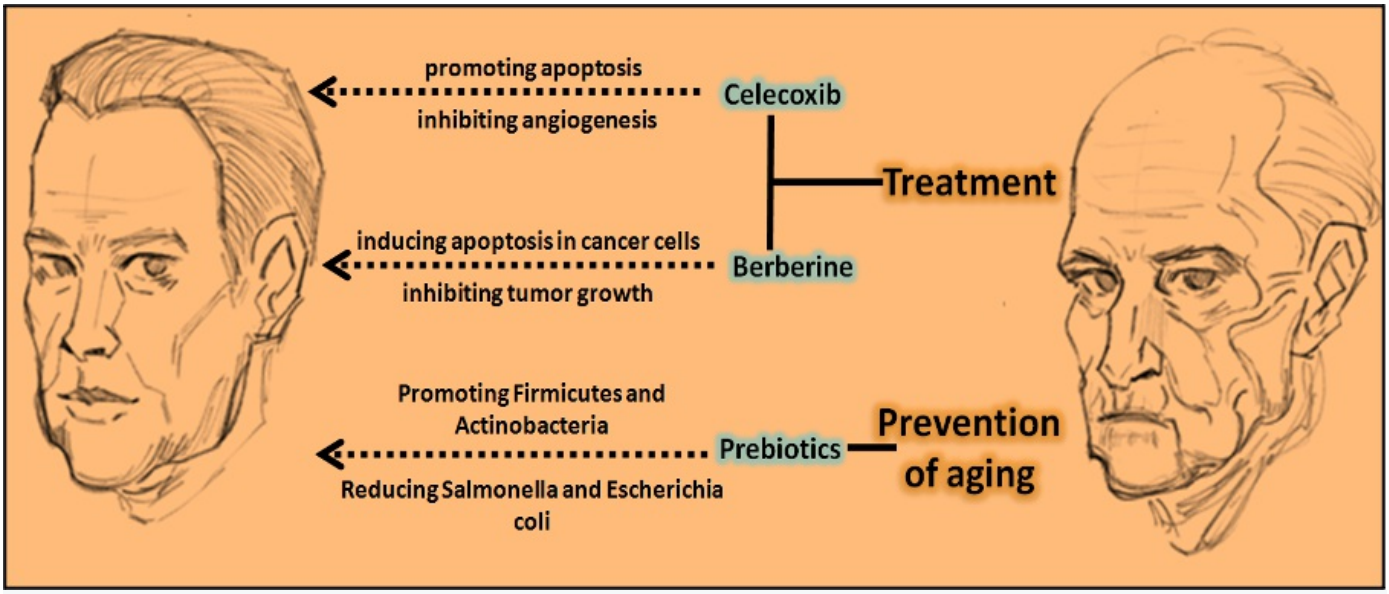

Figure 7. The two strategies for managing the consequences of aging in older people are treating the signs of aging and preventing the signs of aging.

The International Scientific Association for Probiotics and Prebiotics (ISAPP) describes prebiotics as such. Fructans, which are polymers composed of fructose and sucrose, are the main types of prebiotics, with chicory fructans and inulin-type fructans being the most common. Consuming prebiotics can stimulate the growth of beneficial gut bacteria, improving digestion and overall health. Including a variety of prebiotic-rich foods in your diet, such as chicory and inulin-type fructans, can help maintain a healthy gut microbiome. They often contain lactic acid bacteria and other potentially probiotic microorganisms, offering potential health benefits. It is advisable to consult with a healthcare provider before starting any new supplement regimen to ensure safety and effectiveness.

Conclusion

Considering the significance of prebiotics, probiotics, and synbiotics in maintaining gut health as we age, along with the ability of celecoxib to inhibit activated NF-κB and reduce proinflammatory cytokines, it is essential to address the aging process. Incorporating prebiotics, probiotics, and synbiotics into your diet can support gut health and potentially slow down the aging process. Furthermore, the use of anti-inflammatory medications such as celecoxib may also play a role in preventing age-related inflammation and its related complications.

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