Review

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Review

Nutraceutical Strategies for Aging: Looking towards Parkinson's Disease and Frailty

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Abstract: Aging is a complex and inevitable biological process characterized by a gradual decline in physiological function, including increased oxidative stress, chronic inflammation, and mitochondrial dysfunction. While aging is a natural part of life, it is often accompanied by various disorders collectively known as age-related diseases (ARDs) or aging disorders. These include neurodegenerative diseases like Parkinson's (PD), cardiovascular diseases, diabetes, osteoporosis, and frailty, among others. As the global population ages, the prevalence of ARDs such as PD and frailty is rising, necessitating innovative approaches to enhance healthy aging. Nutraceuticals are natural bioactive compounds in foods that offer health benefits beyond essential nutrition, which is pivotal in preventing and managing aging-related disorders. Nutraceuticals, with their antioxidant, anti-inflammatory, and neuroprotective properties, offer promising strategies to counteract these processes and promote healthy aging. This review highlights the potential of nutraceuticals as valuable adjuncts in managing PD and frailty, two conditions intricately linked to ARD. By examining the differential impacts of these bioactive compounds on the underlying mechanisms of each condition, this study underscores the promise of nutraceuticals in promoting healthy aging. The review aims to inform future research and clinical strategies by advocating for developing novel bioactive compounds, using advanced delivery technologies, and integrating personalized approaches based on genetic and epigenetic profiles. These efforts will pave the way for more precise, effective, and individualized interventions, ultimately extending health span and preventing ARD.

Keywords: aging; precision medicine; Parkinson's disease; frailty; nutraceuticals; bioactive compound; physiology and anatomy; anti-oxidant; inflammation

1. Introduction

Over the past decade, the global population has experienced a notable increase in average age, leading to a surge in the elderly demographic [1]. In 2020, the number of individuals aged 70 and older reached approximately 457.96 million worldwide ***(World Population Ageing 2020 Highlights)***. As people live longer, many face significant health challenges, with a majority suffering from one or more chronic, age-related diseases (ARDs) such as cardiovascular diseases, diabetes, neurodegenerative conditions and frailty [2–7].

The prevalence of neurodegenerative disorders like Parkinson's disease (PD), alongside the geriatric syndrome of frailty, has become a significant public health concern [8,9]. PD is a neurodegenerative disorder that manifests clinically through symptoms such as bradykinesia, resting tremor, rigidity, and disturbances in posture and gait, all of which are commonly observed in the elderly [10,11]. In addition to these motor symptoms, PD is also associated with a range of non-motor symptoms, including depression, anxiety, cognitive impairment, and dementia [12–14]. The global prevalence of PD is steadily increasing, with aging identified as a significant risk factor for its onset

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[15]. The physiological changes associated with aging contribute to the disease's development and progression [8]. Frailty, on the other hand, is a geriatric syndrome characterized by a state of increased vulnerability, where an individual's health teeters between robustness and disability [16]. This syndrome is influenced by various physiological stressors accompanying aging and encompasses physical and psychological and social dimensions [17,18]. Both conditions share common pathways related to aging, yet they manifest differently, necessitating more effective and sustainable strategies, including preventive approaches and innovative interventions like nutraceuticals [19–23].

Nutraceuticals, a term coined by Stephen DeFelice, are food-derived products that offer health benefits beyond essential nutrition [24]. They encompass a wide range, including naturally nutrient-rich foods like garlic, isolated nutrients, and herbal products [25–27]. Growing interest is in managing ARDs using nutraceutical bioactive compounds derived from food sources [25]. Nutraceuticals, with their antioxidant, anti-inflammatory, and neuroprotective properties, offer promising adjuncts to conventional treatments [21]. In PD, compounds such as curcumin, resveratrol, and omega-3 fatty acids have shown the potential to slow disease progression and alleviate symptoms by targeting oxidative stress and mitochondrial dysfunction [20].

Similarly, in frailty, these substances may help enhance muscle function, reduce inflammation, and improve overall resilience against physical and psychological stressors [28]. This review aims to explore the distinct effects of nutraceuticals on PD and frailty, evaluating their ability to influence the core mechanisms behind these conditions. Moreover, it underscores the importance of advancing research and clinical approaches, emphasizing the development of novel bioactive compounds, using cutting-edge delivery technologies, and incorporating personalized strategies based on genetic and epigenetic insights. These advancements will contribute to more precise, effective, and individualized treatments, allowing precision medicine to extend health span and mitigate age-related diseases ARDs [29].

2. Aged People Dysfunction: Parkinson's vs. Frailty: A Comparison of Aging-Related Conditions

Aging is a natural and inevitable process that affects every living organism, leading to a gradual decline in physical and cognitive functions [30,31]. As people age, they experience cellular, molecular, and systemic changes, often resulting in various ARDs: increased protein synthesis, apoptosis resistance, and cellular function alterations mark this process [32,33]. The accumulation of senescent cells in tissues becomes more pronounced, leading to a heightened susceptibility to ARDs [34]. For instance, the buildup of senescent cells in joints can result in osteoarthritis, characterized by joint degeneration and impaired mobility [35,36]. Aging also affects various organ systems, leading to physiological changes such as reduced cell turnover, diminished function of mucous membranes, muscle wasting, and a higher risk of conditions like atherosclerosis, contributing to geriatric frailty [37,38]. Cellular senescence, characterized by a progressive decline in physiological function and the release of inflammatory factors, plays a crucial role in aging by hindering tissue regeneration and altering the local environment [39,40]. While interventions targeting senescent cells have shown promise, they can also cause unintended complications, such as elevated urea levels and thrombocytopenia in experimental models [41]. Aging is also linked to the gradual loss of muscle mass and strength (sarcopenia), impaired immune function, and increased vulnerability to infections and other illnesses [42–44].

Cognitive decline, ranging from mild memory lapses to severe forms of dementia, becomes more prevalent with age [45].

Additionally, the aging process is accompanied by reduced physiological resilience, making it harder for elderly individuals to recover from illness, injury, or stress [46,47]. Common conditions associated with aging include neurodegenerative diseases such as PD and frailty [9]. These conditions diminish the quality of life and increase healthcare burdens, as elderly individuals often require more medical care and assistance [31]. Common conditions associated with aging include neurodegenerative diseases such as PD and frailty [9]. These conditions diminish the quality of life

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and increase healthcare burdens, as elderly individuals often require more medical care and assistance [38].

2.1. Parkinson's Disease

PD is a complex neurodegenerative disorder primarily characterized by the loss of dopaminergic neurons in the Substantia Nigra pars compacta (SNpc), and brain accumulation of Lewy bodies (LB), which are aggregates of alpha-synuclein (αS) [12–48]. The diagnosis of PD is based on patient history and neurological examination [49,50]. Although primarily designed for research purposes, the diagnostic criteria established by the International Parkinson and Movement Disorder Society can aid clinicians in confirming the diagnosis [51,52]. The TRAP mnemonic can be helpful in diagnosis, as it includes tremors (T), rigidity (R), akinesia (A), and postural instability (P) [53,54]. However, PD also presents a wide range of less visible, non-motor symptoms, such as cognitive decline, depression, and pain, which contribute significantly to the overall disability experienced by patients [13,14]. These non-motor symptoms can be assessed using a specialized rating scale to quantify their [13,14]. Early indicators include symptoms like constipation (the most common early sign), acting out dreams during REM sleep (indicative of REM sleep behavior disorder), loss of smell (hyposmia), asymmetrical shoulder pain, and depression [55–58]. It is essential to recognize that general practitioners cannot be faulted for missing a diagnosis in the early stages, as these symptoms are often nonspecific and overlap with many other conditions [51,52]. The exact cause of PD remains elusive, but it is believed to result from a combination of genetic predispositions and environmental factors. Mutations in genes such as Leucine-rich repeat kinase 2 (LRRK2), Parkin7 (PARK7), and αSynuclein (αS) have been linked to familial forms of PD, while environmental exposures to toxins, such as pesticides, have been associated with an increased risk of the disease [59–62]. Additionally, mitochondrial dysfunction, oxidative stress, and neuroinflammation are critical contributors to the pathogenesis of PD. These factors lead to the accumulation of reactive oxygen species (ROS), which damage cellular components, further exacerbating neuronal death [63–66].

2.1.1. Current Therapeutic Approaches

Despite the wide range of treatment options, including pharmacological, non-pharmacological, and surgical interventions like brain, spinal, and vagus nerve stimulators, patients still suffer from ongoing muscle weakness, and no therapy has proven to be a definitive disease-modifying solution [67,68].

Conventional Pharmacological Treatments

Levodopa and Derivatives: Levodopa remains a central treatment for PD, converting to dopamine in the brain to alleviate motor symptoms like tremors and [69,70]. Its effectiveness diminishes over time, leading to side effects like dyskinesia [69,70]. Co-administration with carbidopa improves its efficacy and reduces peripheral side effects. However, as the disease progresses, the effectiveness of levodopa diminishes, and patients often experience motor fluctuations and dyskinesias (involuntary movements) [69–71].

MAO-B Inhibitors: Monoamine oxidase B inhibitors delay levodopa breakdown, extending its benefits in early-stage PD [72,73]. Though less potent than levodopa, they pose fewer risks of inducing dyskinesias [71]. These drugs are commonly combined with other therapies to enhance motor symptom management, especially as PD progresses [72–74].

COMT Inhibitors: Catechol-O-methyltransferase inhibitors increase levodopa's availability in the brain by reducing its breakdown [74,75]. Drugs like entacapone and opicapone extend levodopa's effects. However, they may cause adverse effects such as dyskinesia and confusion. Tolcapone, though effective, is rarely used due to the risks of liver failure [74,75].

Anticholinergic Agents: These drugs, including trihexyphenidyl and benztropine, reduce tremors, particularly in younger patients [76,77]. However, their use is limited due to side effects like blurred vision and urinary retention [76,77].

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Non-Conventional Pharmacological Treatments

Antidiabetic Agents: Medications such as glucagon-like peptide 1 (GLP-1) agonists and Dipeptidyl peptidase 4 (DPP-4) inhibitors may offer neuroprotective effects in PD by reducing neuroinflammation and oxidative stress [78–80]. Studies have shown potential benefits in improving motor and cognitive symptoms in PD patients [81].

Intranasal Insulin: Insulin administered intranasally has shown promise in protecting dopaminergic neurons and improving motor function without affecting blood glucose levels [82,83].

Biguanides (Metformin): Though primarily used for type 2 diabetes, metformin has potential neuroprotective effects in PD [84,85]. Some studies suggest it reduces the risk of PD, while others raise concerns about its link to vitamin B12 deficiency, which may contribute to cognitive decline [86].

Non-Pharmacological Treatments

Stem Cell Therapy: Using pluripotent stem cells to regenerate damaged dopaminergic neurons offers a promising future therapy for PD. Early trials using fetal cell transplants have shown long-term benefits but also carry risks like dyskinesia [87–89].

Gene Therapy: Gene therapies targeting defective genes like AADC and neurotrophic factors are being explored to modify disease progression in PD [90,91]. While promising in animal models, clinical application has faced gene distribution and efficacy challenges [90,91].

Surgical Treatments

Lesioning Procedures: Ablative surgeries, like pallidotomy and thalamotomy, target specific brain areas to alleviate motor symptoms [92]. Though effective, these procedures are reserved for patients unresponsive to medication, with risks of neurological side effects [92].

Deep Brain Stimulation (DBS): DBS is widely used to control PD motor symptoms by delivering electrical impulses to the brain [93,94]. It improves motor function and reduces reliance on medications, though it requires careful management to avoid side effects like dyskinesia and cognitive impairment [93,94].

Focused Ultrasound (FUS): FUS is a non-invasive method that uses ultrasound waves to target deep brain tissues, offering a promising alternative to traditional surgery for motor symptom relief in PD [95].

Gamma Knife Thalamotomy (GKT): GKT uses targeted gamma radiation to treat tremors in PD. It is minimally invasive, with fewer long-term complications, though risks such as radiation-induced neurological changes remain [96,97].

2.1.2. Limitations of Conventional Treatments

Despite the availability of various treatments for PD, limitations and side effects persist across both pharmacological and non-pharmacological approaches [98]. Levodopa, a cornerstone therapy that converts to dopamine to alleviate motor symptoms like tremors and rigidity, loses effectiveness over time and can lead to side effects such as dyskinesia and motor fluctuations [99]. While MAO-B inhibitors help delay levodopa's breakdown and extend its benefits, they are less potent and usually require a combination with other treatments [100]. COMT inhibitors increase levodopa availability but may induce dyskinesia and confusion, with some drugs, like tolcapone, posing risks of liver failure [101]. Anticholinergic agents, used for tremor control, particularly in younger patients, come with side effects like blurred vision and urinary retention, limiting their use [102]. Non-conventional pharmacological treatments also present challenges [98]. Antidiabetic agents like GLP-1 agonists and DPP-4 inhibitors show potential for reducing neuroinflammation, but their off-target effects remain under investigation [103]. Intranasal insulin may protect dopaminergic neurons and improve motor function, though it is still in early-stage research [103]. Metformin, an antidiabetic drug, has been associated with a reduced risk of PD but raises concerns about vitamin B12 deficiency and possible cognitive decline. Non-pharmacological and surgical options carry their risks [104,105]. Stem cell therapy offers promise for regenerating dopaminergic neurons but carries the risk of dyskinesia and

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ethical challenges [106]. Gene therapy faces obstacles in gene distribution and efficacy in clinical applications [107]. Surgical approaches, like lesioning procedures, are reserved for patients unresponsive to medication and come with neurological side effects [108]. DBS, although effective in controlling motor symptoms, can lead to dyskinesia and cognitive impairment [109]. Newer techniques, like FUS and GKT, offer less invasive alternatives, though they carry risks of tissue damage and radiation-induced neurological changes [110] (Table1).

Table 1. Overview of Therapeutic Approaches for PD.

Category	Treatment	Mechanism	Benefits	Limitations/ Side Effects	Ref
Conventional Pharmacological Treatments	**Levodopa and Derivatives**	Converts to dopamine to alleviate motor symptoms	Effective for tremors and rigidity	Diminished effectiveness over time, dyskinesia, motor fluctuations	[69–71]
	MAO-B Inhibitors	Delays breakdown of levodopa, extending benefits	Fewer dyskinesias, used in early-stage PD	Less potent than levodopa, often used in combination with other therapies	[69–74]
	COMT Inhibitors	Increases levodopa availability by reducing breakdown	Extends levodopa's effects	Dyskinesia, confusion, tolcapone risk of liver failure	[101]
Non-Conventional Pharmacological Treatments	**GLP-1 DPP-4**	It may reduce neuroinflammation and oxidative stress	Potential neuroprotective effects, motor and cognitive improvements	Potential off-target effects; still under study	[78–81]
	Intranasal Insulin	Protects dopaminergic neurons and improves motor function	No effect on blood glucose levels	Early-stage research requires further clinical validation	[82,83]
	Biguanides (Metformin)	Potential neuroprotective effects	Neuroprotective effects in PD	Risk of vitamin B12 deficiency, potential cognitive decline	[84–86]
Non-Pharmacological Treatments	**Stem Cell Therapy**	Regenerates dopaminergic neurons	Long-term motor benefits	Risks of dyskinesia, ethical concerns, early-stage research	[87–89]
	Gene Therapy	Targets defective genes and neurotrophic factors	Promising disease-modifying potential	Gene distribution challenges, efficacy concerns in clinical application	[90–92]
	Lesioning Procedures	Targets specific brain areas to alleviate motor symptoms	Effective for motor symptom relief	Neurological side effects, reserved for medication-unresponsive patients	[92]

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Surgical Treatments	**DBS**	Delivers electrical impulses to control motor symptoms	Improves motor function, reduces medication reliance	Risk of dyskinesia and cognitive impairment requires careful management	[93,94]
	FUS	Non-invasive ultrasound to target brain tissue	A promising alternative to traditional surgery	Still under study, the potential for tissue damage	[95]
	GKT	Uses gamma radiation to treat tremors	Minimally invasive, fewer long-term complications	Radiation-induced neurological changes possible	[96,97]

2.2. Frailty

Frailty is a clinical syndrome characterized by a reduction in physiological reserve and increased vulnerability to stressors, leading to adverse health outcomes such as falls, hospitalization, disability, and death [111,112]. It is often seen in older adults and is associated with a decline in multiple body systems [111,112]. Clinically, frailty is diagnosed using criteria like the Fried Frailty Phenotype, which includes unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity [113,114]. Three or more criteria indicate frailty, while one or two suggest a pre-frail state [115,116]. Frailty is not merely a consequence of aging but a distinct clinical entity that significantly impacts an individual's quality of life and functional independence [115,116]. It is associated with a higher risk of adverse outcomes, particularly in the presence of acute illnesses or surgical interventions [117]. The pathophysiology of frailty is multifaceted, involving complex interactions between various biological systems [111,112]. Chronic inflammation plays a central role, with elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNFα) contributing to muscle catabolism, reduced muscle mass and strength, a condition known as sarcopenia, which is a core component of frailty [118–120].

Additionally, hormonal imbalances, including decreased levels of anabolic hormones like testosterone and growth hormone, exacerbate the decline in muscle and bone health [121]. Mitochondrial dysfunction is also critical in frailty, leading to decreased energy production and increased oxidative stress, further accelerating cellular aging and tissue damage [122]. Additionally, frailty is associated with insulin resistance, dysregulated glucose metabolism, and impaired autophagy, all contributing to the decline in cellular and systemic resilience [123].

2.2.1. Current Therapeutic Approaches

Patients affected by the clinical syndromes of frailty have limited options to effectively slow disease progression outside of exercise training [124]. Given the difficulty in reversing disability in older adults, its impact is both severe for individuals and costly for society [125]. Therefore, developing new strategies to maintain functional capacity and independence in later life is crucial, particularly in chronic illness [126]. A combined approach involving exercise, nutrition, and pharmacological interventions may help mitigate the onset and progression of frailty [126].

Drug Therapy

Hormone Therapies: Among the potential pharmacological treatments extensively studied in preclinical settings are hormone therapies and myostatin inhibitors [127]. Hormone therapies include the administration of testosterone, growth hormone (GH), ghrelin, insulin, and thyroid hormones [128–131].

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Testosterone replacement therapy, given its known metabolic and anabolic effects, has been explored as a possible treatment for frailty [132]. Clinical trials have shown that testosterone can modestly improve muscle function and overall physical capacity in frailty patients [133,134]. However, side effects like the risk of prostatic hyperplasia necessitate further large-scale studies to validate its safety and efficacy [133,134]. While showing promise in preclinical studies for its anabolic, anti-inflammatory, and antioxidant benefits, GH therapy has yet to demonstrate clinical effectiveness [135]. Ghrelin is another potential treatment due to its ability to stimulate appetite and enhance gastric motility [136].

Insulin: Increasing amino acid delivery and intramuscular blood flow promotes muscle protein synthesis [137]. Thyroid hormone, a critical metabolic regulator targeting skeletal muscle, has been linked to muscle wasting and diminished function in overt and latent thyroid dysfunction cases [138].

Myostatin: Myostatin, a cytokine within the Transforming growth factor-β (TGF-β) family, is highly expressed in skeletal muscles and regulates muscle growth [139,140]. However, several trials of myostatin inhibitors have yielded underwhelming results, showing limited therapeutic benefit [141]. Nevertheless, a study involving bimagrumab, a myostatin inhibitor, demonstrated positive outcomes, improving functional capacity and independence in elderly sarcopenic individuals [142].

GDF-15: Another promising target has recently gained attention: growth differentiation factor 15 (GDF-15), a key regulator in muscle pathophysiology and a global stress mediator [143,144]. Evidence indicates that GDF-15 is associated with reduced muscle mass, impaired performance, and heightened inflammation [145]. Neutralizing GDF-15 has shown promise in reversing these effects, helping to restore muscle function and physical capacity [146]. In experimental models, anti-GDF-15 treatment significantly increased muscle mass by boosting appetite and food intake, improving physical function [147].

Exercise: Exercise is now recognized as the most effective therapy for slowing the progression of frailty [148,149]. Well-structured and closely supervised exercise training programs are designed to combat muscle atrophy, stimulate muscle growth, and preserve muscle function as individuals age [148,149]. Resistance exercise benefits muscle health through various physiological mechanisms and signaling pathways, including vasodilation, antithrombotic effects, reduced oxidative stress, anti-inflammatory responses, activation of mechanistic target of rapamycin complex-1 (mTORC1), enhanced mitochondrial biogenesis, increased Insulin-like Growth Factor 1 (IGF-1), stimulation of peroxisomes, and improved insulin sensitivity [150,151]. These molecular adaptations show that skeletal muscle is highly responsive and adaptable to activity. Low-intensity training enhances mitochondrial efficiency and oxygen utilization, while high-intensity exercise stimulates muscle cell proliferation and increases contractile protein production [152]. Exercise also upregulates gene transcription related to calcium (Ca2+) signaling via the Adenosine monophosphate-activated protein kinase (AMPK) pathway, influencing the energy status of muscle cells [153].

Nutrition: Malnutrition encompasses various forms of undernutrition, such as wasting, stunting, underweight, vitamin and mineral deficiencies, obesity, and related non-communicable diseases [154]. Nutritional deficiencies in micronutrients (e.g., vitamins and minerals) and macronutrients (such as energy stores and substrates) contribute to a worsening catabolic state in conditions like frailty [155–157]. For example, vitamin D deficiency can impair muscle function, alter calcium flow, and promote inflammation. However, it also reduces muscle mass and poor physical performance in older adults [158]. Consequently, vitamin D supplementation is potentially a therapeutic option for managing frailty [159,160]. New insights into the link between muscle health and nutrition reveal that proper nutrition supports muscle function, stimulates muscle growth (anabolism), and regulates muscle protein synthesis, glucose, insulin levels, and neuromuscular and vascular functions [161]. Nutrition also plays a crucial role in nutrient sensing, mitochondrial efficiency, and communication between muscles and the immune system. When combined, nutritional interventions and exercise can have additive effects, particularly when resistance training is paired with protein supplementation, improving muscle mass and function [162]. Dietary protein is vital for maintaining muscle structure, function, and a healthy balance between anabolic and catabolic processes in frail elderly individuals [163]. Essential amino acids, like leucine, trigger strong

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anabolic responses by activating muscle signaling pathways that enhance mRNA translation and muscle protein synthesis [164]. Omega-3 polyunsaturated fatty acids also offer a potential benefit due to their anti-inflammatory properties [165]. Despite their crucial role in managing frailty, nutritional interventions face challenges. These include the complexity of food and nutrient interactions, difficulty in blinding treatments, low patient adherence, and the influence of factors like ethnicity, genetics, and physiological condition, along with dietary habits and food culture variations [154].

2.2.2. Limitations of Conventional Treatments

Pharmacological and nutritional interventions for treating frailty have notable limitations and potential side effects [166]. Testosterone therapy, despite its ability to improve muscle function, carries risks such as prostatic hyperplasia, necessitating large-scale trials to confirm its safety [167]. Though promising in preclinical studies, GH treatment has yet to demonstrate clinical efficacy [128–131]. Ghrelin and insulin therapies, while showing potential in improving muscle function and protein synthesis, may pose risks, with insulin linked to poorer outcomes in heart failure (HF) patients with diabetes [136]. Thyroid hormone interventions face challenges in managing muscle wasting, particularly in cases of thyroid dysfunction [167]. Myostatin inhibition trials, including those with bimagrumab, have yielded limited therapeutic benefits, and further research is needed [168]. Nutritional interventions like protein and vitamin D supplementation also require careful consideration, particularly in frail patients with chronic kidney disease or heart failure [169]. Additionally, compliance with dietary interventions remains low, and factors like ethnicity, genetics, and food culture introduce significant variability, making treatment outcomes less predictable [170]. **(Table2)**.

Table 2. Overview of Therapeutic Approaches for Frailty.

Category	Treatment	Mechanism	Benefits	Limitations/ Side Effects	Ref
Hormone Therapy	**Testosterone**	Increases anabolic and metabolic activity, promoting muscle growth and improving physical capacity.	Modestly improves muscle function and overall physical capacity in frailty patients.	Requires large-scale studies for safety and efficacy validation. Risk of prostatic hyperplasia.	[132–135]
	GH	Anabolic, anti-inflammatory, and antioxidant effects in preclinical models.	Shows promise in preclinical studies for muscle growth and function.	Has not demonstrated clinical effectiveness.Uncertain due to lack of clinical efficacy data.	[127]
	Ghrelin	Stimulates appetite and enhances gastric motility.	Potential to improve muscle mass and nutritional status by stimulating appetite.	Clinical benefits are not fully validated.	[136]
	Insulin	Promotes muscle protein synthesis by	It enhances muscle protein	Associated with poorer outcomes in heart failure patients with diabetes. Risk	[137]

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		increasing amino acid delivery and blood flow to muscles.	synthesis and may prevent muscle wasting.	of adverse effects in patients with heart failure.	
	Thyroid Hormone	Critical metabolic regulator affecting skeletal muscle.	Linked to improved muscle metabolism and function.	Limited effectiveness in cases of overt and latent thyroid dysfunction. Potential to worsen muscle wasting in thyroid dysfunction cases.	[138]
	Myostatin	Blocks myostatin, a cytokine that regulates muscle growth, to promote muscle mass increase.	Positive outcomes in improving muscle function and independence in elderly sarcopenic individuals.	Limited therapeutic benefit in many clinical trials. Unknown due to limited clinical success.	[139–142]
	GDF-15	Neutralizing GDF-15, associated with reduced muscle mass and heightened inflammation, restores muscle function.	Significantly increases muscle mass, boosts appetite, and improves physical function in experimental models.	Experimental requires further validation in clinical settings.	[145–147]
Exercise	**Resistance Training**	Involves mTORC1 activation, mitochondrial biogenesis, increased IGF-1, and enhanced insulin sensitivity, reducing oxidative stress and inflammation.	Preserves and enhances muscle mass, strength, and function in frail individuals.	Requires structured programs and close supervision, making adherence challenging.Risk of injury in frail patients if not appropriately supervised.	[148–153]
Nutrition	**Vitamin D**	Regulates calcium flow and reduces inflammation, impacting muscle function.	May improve muscle mass and physical performance in older adults with deficiency.	Effectiveness limited by patient adherence and variability in dietary habits.Uncertain in patients with chronic kidney disease or heart failure.	[158–160]

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Protein	Stimulates muscle protein synthesis and anabolism, particularly through essential amino acids like leucine. and inflammation.	Helps maintain muscle structure and function, and improves muscle mass in frail elderly individuals	Compliance issues due to variability in diet, ethnicity, and genetics.	[161]
Omega-3 Fatty Acids	Anti-inflammatory properties that support muscle health.	May reduce inflammation and support muscle function in frailty.	Challenges include low adherence and complex interactions with other nutrients	[165]

3. Unvelling the differences: Nutraceutical vs. Conventional Food

Interest in nutraceuticals and functional foods is rising, driven by ongoing research into their properties and applications and increasing consumer demand [171,172]. Nutraceuticals or functional foods are often viewed as "foods that resemble conventional items in the diet and are consumed regularly but offer additional benefits beyond basic nutrition [171,172]. These benefits may include reducing the risk of chronic diseases or improving overall health, with generally lower toxicity than synthetic drugs" [173]. Understanding the distinction between "functional foods" and "nutraceuticals" is crucial [174,175]. The concept of functional foods began in Japan in the late 1970s, driven by an aging population and increasing health concerns [176]. This led to a national project for systematic food research and development, culminating in the establishment of the Food for Specified Health Use (FOSHU) policy by the Ministry of Health and Welfare (MHW) in 1991 [177]. FOSHU foods were defined as "foods that contribute to health maintenance based on scientific data related to food components and consumer health" [177]. The first FOSHU product, a hypoallergenic food, was approved in 1993, and by 2001, the market had expanded significantly, with 192 products gaining approval [178]. The concept gained international attention following a 1993 article, "Japan explores the boundary between food and medicine," marking the first use of functional foods and highlighting the sector's rapid growth in the US [179]. In the United States of America (U.S.A), functional foods are regulated under the Federal Food, Drug, and Cosmetic (FD&C) Act and the Dietary Supplement Health and Education Act (DSHEA), overseen by the Food and Drug Administration (FDA) [180,181]. These products are categorized as nutraceuticals, dietary supplements, or conventional foods but not as medicines [182]. In Europe, various agencies regulate functional foods and provide scientific support. *Functional foods* are "products that demonstrate beneficial effects on one or more body functions beyond basic nutrition, improving health and reducing disease risk" [183–185]. The regulatory framework includes the Framework Directive (90/496/CEE) and the General Food Law [Regulation (EC) 178/2002], which set standards for labeling and health claims [183,184,186]. Regulatory agencies and researchers generally agree that functional foods are consumed as part of a regular diet and offer health benefits beyond essential nutrition [171,172]. Some definitions of nutraceuticals specify that they are formulated products taken in specific doses (e.g., capsules, pills, or tablets) [187]. Others consider functional foods to supply essential nutrients like vitamins, proteins, and carbohydrates [187]; however, when these foods provide additional health benefits such as disease prevention or treatment, they are classified as nutraceuticals, even if consumed as ordinary food [188]. Functional foods can originate from common foods containing naturally occurring bioactive substances (e.g., dietary fiber) [189] , from foods enriched with bioactive compounds (e.g., probiotics and antioxidants) [190], or from ingredients derived from certain foods that are added to

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other conventional foods (e.g., prebiotics) [191]. Several factors contribute to the expanding functional food market, notably current population and health trends [171,172]. Globally, populations are aging, with life expectancy continuing to rise and older adults comprising a growing segment [192]. Additionally, obesity has become a worldwide concern, with its prevalence increasing in many countries [193]. Individuals take dietary supplements and consume foods formulated or fortified with health-promoting components to enhance health outcomes [194]. This trend is also supported by increased public education, as people today are more knowledgeable about nutrition than ever before, with their growing interest in health-related information being addressed through various educational resources [194]. The growing interest in nutraceuticals stems from their potential for improved quality of life, addressing modern challenges and consumer demand for alternatives [195]. Regardless of their origin, these compounds can provide various health benefits, from antioxidant and anti-inflammatory properties to supporting specific health conditions [196]. Despite their potential, nutraceuticals face several challenges. Their diverse composition and varied modes of action make it difficult to develop standardized delivery methods [197]. Additionally, low bioavailability and potential interactions with other food components hinder their practical use [197]. Researchers are exploring encapsulation technologies [197]. Encapsulating nutraceuticals within protective structures can improve their stability, solubility, and bioavailability [198,199]. Various methods, including micro and nano-encapsulation, are being investigated to optimize the delivery of these valuable compounds [198,199]. Ultimately, nutraceuticals' successful development and utilization depend on a clear understanding of their properties, effective delivery systems, and robust regulatory frameworks [197].

3.1. Categories of Nutraceuticals: A Comprehensive Overview

Nutraceuticals are categorized according to their applications into various classes, including traditional, non-traditional, fortified, recombinant, phytochemicals, herbal products, functional foods, dietary supplements, probiotics, and prebiotics [200]. Each class of nutraceuticals offers distinct applications and benefits, depending on its specific characteristics [200]. The classification of nutraceuticals often overlaps, as their chemical composition and health-promoting functions are similar [188]. According to the Institute of Food Technologists (IFT), *functional foods* are "foods and food components that provide a health benefit beyond basic nutrition" [201]. This category includes conventional foods, fortified, enriched, enhanced, and dietary supplements [200].

3.1.1. Traditional Nutraceuticals

Functional Foods

Functional foods contain ingredients that enhance antioxidant and anti-inflammatory activities [176,184]. Examples include rice, wheat, beans, soybeans, lentils, chocolate, citrus fruits, nuts, and fermented milk [176,184]. Rice, for instance, is a staple food rich in carbohydrates and low in fat, salt, and sugar. It also contains resistant starch, which supports gut health [202]. Similarly, wheat is valued for its fiber-rich bran, which promotes gastrointestinal health [203]. Other examples, like carrots and broccoli, contain active components such as sulforaphane and lycopene, which are known for their health benefits [204]. However, more scientific studies are needed to validate these product labels' health claims.

Carotenoids: carotenoids are natural pigments found in plants, fruits, vegetables, and algae, known for their antioxidant and anti-inflammatory properties [205]. These compounds, including β-carotene and lutein, offer various health benefits, such as improving vision, cognitive function, and heart health, while helping prevent cancer [206]. Their antioxidant activity is due to their chemical structure, which allows them to neutralize free radicals [176,184,205,206].

Collagen Hydrolysate: collagen hydrolysate, derived from collagen found in animal connective tissues, has several health benefits, including antioxidant, anti-aging, and anti-inflammatory effects [207,208]. Studies have shown that collagen hydrolysate can boost the immune system, improve skin hydration elasticity, and reduce wrinkles, especially in cases of photoaged skin [209,210].

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Dietary Fibers: dietary fibers are non-digestible carbohydrates in vegetables, fruits, and whole grains [203]. They are classified into soluble and insoluble fibers, each offering specific health benefits [211]. For example, soluble fibers can help manage digestive health by delaying gastric emptying, while insoluble fibers can alleviate constipation [203]. High-fiber diets are also linked to a reduced risk of inflammatory bowel diseases [203].

Fatty Acids: fatty acids in oils, fats, and fish supplements are crucial for energy storage and offer anti-inflammatory and immune-boosting benefits [212]. Omega-3 polyunsaturated fatty acids (PUFAs), in particular, have been shown to reduce the severity of symptoms in conditions like rheumatoid arthritis when taken in sufficient doses [213] .

Phytochemicals: phytochemicals are bioactive compounds derived from plants that support various biochemical and metabolic functions in the body [214]. They offer neuroprotective benefits and can reduce the risk of cancers, heart disease, and neurodegenerative disorders through their antioxidant properties [214].

Herbs: herbs like garlic, ginger, and aloe have been used for centuries for their health benefits, which include reducing cholesterol, promoting wound healing, and offering antioxidant properties [215]. The effectiveness of herbs can vary depending on how they are processed and consumed [215].

Probiotics: Probiotics are beneficial microbes commonly found in fermented foods, especially dairy products, that promote digestive health and support the immune system [216]. Lactobacillus, Bifidobacterium, and Streptococcus are among the most commonly used probiotic strains known to maintain a healthy balance of gut bacteria [216].

Prebiotics: prebiotics are non-digestible ingredients that stimulate the activity of probiotics in the gut [217]. They act as a fertilizer for beneficial gut bacteria, enhancing the health benefits provided by probiotics [218]. Fructo-oligosaccharides and inulin are prebiotics used in functional foods to improve digestive health [219].

Dietary Supplements: dietary supplements, available in various forms like tablets, capsules, and powders, are intended to supplement the diet and ensure adequate nutrient intake [220]. Joint supplements include omega-3 fatty acids, vitamins, and minerals, which can prevent nutrient deficiencies and support overall health [221,222].

3.1.2. Non-Traditional Nutraceuticals

Non-traditional nutraceuticals are artificially synthesized food products that enhance health through biotechnology and agricultural breeding [200]. Based on their processing, these nutraceuticals can be categorized into fortified and recombinant types [200]. Examples include rice enriched with β-carotene and cereals fortified with vitamins and minerals, which boost antioxidant activity and provide essential nutrients like provitamin A [200].

Fortified Nutraceuticals: Fortified nutraceuticals are foods enhanced with additional vitamins or micronutrients to improve their nutritional value [223]. For instance, orange juice fortified with calcium or milk enriched with vitamin D helps prevent deficiencies and support overall health [224]. Such products can also offer specific benefits, like enhanced glycemic control when calcium is added to orange juice [225].

Recombinant Nutraceuticals: *Recombinant nutraceuticals* are genetically modified foods created through biotechnology to include beneficial compounds [188,226]. Examples include iron-fortified rice, golden rice, and multivitamin corn [227]. These products contain genes that enhance their nutritional content, such as increasing levels of vitamins, carotenoids, and proteins [228,229]. Gold kiwifruit, for example, has been modified to boost its vitamin C, carotenoid, and lutein content, making it a rich source of essential nutrients [230].

4. Mechanisms of Nutraceutical Action in Frailty and Parkinson's Disease

Nutraceuticals are believed to enhance human health, extend life expectancy, and delay the onset of aging and chronic diseases [231]. Numerous nutraceutical supplements have positively affected conditions like PD and frailty [22,232]. Their ability to address oxidative stress, inflammation,

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mitochondrial dysfunction, and protein aggregation underscores their potential as complementary strategies in promoting healthy aging and mitigating disease progression [233].

4.1. Anti-Inflammatory Activity

Nutraceuticals are known for their anti-inflammatory properties, which are crucial in preventing and treating diseases associated with chronic inflammation [234]. One significant advantage of using nutraceuticals as anti-inflammatory agents is that they can complement traditional anti-inflammatory drugs, allowing for lower drug dosages and reducing potential side effects [235]. Chronic inflammation is a leading cause of several major diseases, including frailty and PD [236,237]. Nutraceuticals can help mitigate this inflammation by suppressing inflammatory cytokines like interleukins, Tumor Necrosis Factor-alpha (TNF-α), and cyclooxygenase-2 (COX-2) [238]. For example, curcumin, the active compound in turmeric, has potent anti-inflammatory properties. It works by inhibiting key inflammatory pathways, including the Nuclear factor kappa B (NF-κB) and COX-2 pathways, and reducing the production of pro-inflammatory cytokines like TNF-α, interleukins-6 (IL-6), and IL-1β. These cytokines are implicated in muscle degradation and systemic inflammation in frailty [239,240]. Despite its apparent pharmacokinetic limitations, curcumin, a well-known anti-inflammatory compound, has been shown to exhibit a wide range of pharmacological activities and demonstrate effectiveness against numerous diseases [241]. These include its anticarcinogenic effects [242], hepatoprotective properties [243], thrombosuppressive action [245], cardioprotective benefits [245], antiarthritic effects [246], and its role in combating infections [247]. The study of the chemical biology of aging is expected to reveal candidate compounds and fundamental mechanisms that will drive the development of treatments for age-related diseases [248]. Curcumin exemplifies this concept due to its multiple in vitro benefits. It has been shown to extend lifespan in *C. elegans* and *Drosophila*, although similar effects have not been observed in mice [249,250]. Still, considerable evidence suggests that curcumin may aid in treating neurodegenerative and other age-related diseases, potentially enhancing health span [251]. Polyunsaturated fatty acids (PUFAs) are another class of nutraceuticals that effectively manage inflammatory disorders: docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are known to reduce inflammation by inhibiting the production of pro-inflammatory cytokines and eicosanoids such as prostaglandins and leukotrienes [252]. They also promote the production of specialized pro-resolving mediators (SPMs) like resolvins and protectins, which help resolve inflammation [253]. PUFA treatment has been shown to decrease the expression of NF-κB and reduce proinflammatory markers while increasing anti-inflammatory markers like IL-10 in patients with conditions such as Duchenne muscular dystrophy [254].

Additionally, DHA has demonstrated neuroprotective effects in various animal models of neurodegenerative diseases [255,256]. While there is less research on DHA consumption and its impact on PD, recent epidemiological studies suggest that a high intake of unsaturated fatty acids may lower the risk of developing PD and offer protection against pesticide-induced neurotoxicity [255,256]. Research in the MPTP animal model of PD has also highlighted the protective effects of PUFAs against MPTP-induced neurotoxicity [257]. Although the exact mechanisms behind these effects are not fully understood, several studies have shown that PUFAs enhance the release of neurotrophic factors, regulate genes involved in oxidative stress and apoptosis, and reduce inflammation associated with PD [258].

Polyphenols are bioactive compounds in fruits, vegetables, and teas [259,260]. They exhibit intense anti-inflammatory and antioxidant activities by modulating signaling pathways like NF-κB and Nrf2 and reducing oxidative stress [259,260]. Resveratrol in red grapes and quercetin in apples and onions inhibit inflammatory mediators and support muscle health [259,261]. Indeed, it activates SIRT1 and improves mitochondrial function, protecting against cognitive decline [262].

Lycopene (LYC), a natural carotenoid pigment primarily found in red fruits and vegetables such as tomatoes, papayas, pink grapefruits, pink guavas, and watermelons, has gained significant attention for its diverse biological activities [263,264]. LYC is an unsaturated acyclic carotenoid with 11 linear conjugated and two non-conjugated double bonds [265]. Studies have demonstrated that

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LYC exhibits potent antioxidant and anti-inflammatory properties both in vitro and in vivo, and it can also cross the blood-brain barrier [266,267]. Furthermore, higher serum levels of carotenoid pigments like lycopene, lutein, and zeaxanthin have been associated with a reduced risk of neurodegenerative diseases [268].

The discovery of a proinflammatory shift in the gut microbiota associated with PD and its potential involvement in the progression of this neurodegenerative disorder has sparked interest in exploring gut microbiota-modulating treatments, such as probiotics, as possible therapeutic options for PD [12,269]. Probiotics provide these health benefits through various mechanisms, such as restoring balance to a disrupted intestinal microbiome [270], enhancing the function of the intestinal barrier [271], and activating enzymes that produce metabolites, which help regulate both peripheral and central energy metabolism and inflammation, in addition to promoting neurogenesis, neurotransmission, and even behavioral changes [272].

Animal studies of PD, for instance, have demonstrated that probiotics can lower levels of inflammatory cytokines like IL-1β and IL-6, which in turn helps prevent neuroinflammation [273]. Indeed, probiotics exhibit anti-inflammatory effects by modulating the NF-κB signaling pathway, inflammatory cytokines, and the regulatory T-cell response [274]. A combination of probiotics such as *Lactobacillus rhamnosus*, *Bifidobacterium lactis*, and *Bifidobacterium longum* has been shown to induce IL-10 production and reduce proinflammatory cytokines [275,276]. Prebiotics, like β-(1,3)-glucan, also demonstrate anti-inflammatory and immunomodulatory effects [277]. In animal studies, pre-treatment with β-(1,3)-glucan prevented symptoms of inflammatory bowel disease and inhibited inflammatory cytokines and reactive oxygen species (ROS) [278].

Other nutraceuticals, including ginger, cinnamon, and peppermint, also possess potent anti-inflammatory activities [279]. Emerging evidence from both in vivo and in vitro studies highlights the neuroprotective properties of ginger and its vital active components, zingerone, 6-shogaol, and 6-gingerol, in PD [280]. These protective effects are primarily linked to the regulation of neuroinflammation, oxidative stress, intestinal permeability, dopamine synaptic transmission, and potentially mitochondrial dysfunction [280]. Several transcription factors and signaling pathways are involved in mediating these benefits, including NF-κB, p38 mitogen-activated protein kinase (MAPK), phosphatidylinositol-3-kinase (PI3K)/Akt, extracellular signal-regulated kinase (ERK) 1/2, and AMP-activated protein kinase (AMPK)/proliferator-activated receptor gamma coactivator one alpha (PGC1α) [281]. These pathways contribute to ginger's neuroprotective effects in PD [282].

Cinnamon and peppermint extracts have similarly shown strong anti-inflammatory effects by significantly reducing the expression of inflammatory cytokines IL-1 and IL-6 in experimental animal models and individuals with various CNS complications like PD and frailty [283].

Ginkgolides, bioactive compounds derived from the Ginkgo biloba tree, have been used in traditional Chinese medicine for centuries [283]. Extensive research has validated their neuroprotective properties, making them a valuable component of treatments for various neurological disorders, including PD [283]. Ginkgolides exert a multifaceted influence on the CNS. They modulate neurotransmitter activity, such as glutamate and dopamine, and inhibit platelet-activating factors (PAF), a critical inflammatory mediator [283]. These actions contribute to their neuroprotective effects [283].

4.2. Anti-Oxidant Activity

Curcumin increases antioxidant defense mechanisms by upregulating transcription and expression levels of antioxidant enzymes and improving mitochondrial function [284]. Studies in vitro showed that curcumin presented senolytic properties with reduced hallmarks of senescence (i.e., p16, IL-6, IL-8, MMP3, and MMP13) [285]. However, curcumin has lower bioavailability, compromising its senolytic activity [286]. Combining piperine, alginates, or nanocapsules improves its stability and bioavailability [287]. PD is characterized by a chronic, low-grade inflammatory process in which activated microglia release cytotoxic compounds, most notably peroxynitrite, that contribute to the death and dysfunction of nearby dopaminergic neurons [288]. As neurons die, they release damage-associated molecular pattern proteins like high mobility, activating microglia

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through various receptors, amplifying the inflammatory response [289]. Since peroxynitrite is central to this destructive cycle, nutraceutical approaches that either reduce microglial peroxynitrite production or enhance the scavenging of peroxynitrite-derived oxidants could be valuable for preventing and managing PD [289]. Peroxynitrite formation can be mitigated by inhibiting microglial NADPH oxidase activity, which produces its precursor, superoxide, or by down-regulating signaling pathways that stimulate microglial expression of inducible nitric oxide synthase (iNOS) [289]. Nutrients and compounds such as phycocyanobilin from spirulina, ferulic acid, long-chain omega-3 fatty acids, adequate vitamin D levels, hydrogen sulfide-promoting substances like taurine and N-acetylcysteine, caffeine, epigallocatechin-gallate, butyrogenic fiber, and probiotics may help reduce microglial iNOS induction [289].

Additionally, scavenging peroxynitrite-derived radicals can be enhanced through supplementation with zinc or inosine. Astaxanthin may protect the mitochondrial respiratory chain from peroxynitrite damage and environmental toxins [288]. Plant-based diets low in protein and possibly diets rich in corn and spermidine might offer protection by enhancing mitophagy and supporting mitochondrial health.

Furthermore, low-protein diets can help maintain a more stable response to levodopa therapy [288]. Exogenous antioxidants like vitamins C, E, and phenolic compounds are crucial in neutralizing free radicals [291]. In contrast to traditional antioxidants like vitamins C, E, and β-carotene, natural compounds such as flavonoids (quercetin, curcumin, luteolin, and catechins) and magnolol/honokiol have demonstrated superior efficacy in inhibiting oxidative processes in various in vitro and in vivo models of aging and PD [291] : vitamin C is highly effective at scavenging harmful free radicals such as hydroxyl and superoxide anion radicals and helps protect cells and DNA from oxidative damage [292]. Alongside vitamin C, vitamin E also contributes to safeguarding cells by preventing lipid peroxidation [293].

Gingerols, the bioactive compounds found in ginger, have demonstrated various neuroprotective properties, including antioxidant and anti-amyloidogenic [294]. 6-Gingerol, a key component of ginger, has been shown to inhibit astrocyte overactivation and reduce inflammation in microglia [295]. Both environmental and genetic factors, including iron accumulation and oxidative stress, contribute to PD development [60]. Through its active compounds, ginger may offer potential benefits for individuals with PD [280]. Ginger could potentially mitigate cognitive dysfunction associated with this condition by inhibiting inflammation, increasing nerve growth factor, and promoting synapse formation [280]. In conclusion, the antioxidant properties of nuts offer a promising approach to mitigating the health challenges associated with aging, making them a valuable dietary addition for older individuals [296].

Saffron, a prized spice derived from the Crocus sativus plant, has long been valued for its culinary and cosmetic applications [297]. Recent research has unveiled its potential therapeutic benefits, particularly in neurological disorders [297]. Saffron's antioxidant properties have shown promise in mitigating the effects of neurodegenerative conditions [297]. Saffron and its components have been found to enhance antioxidant defenses against reactive oxygen species, lipid peroxidation, and other oxidative damage [297]. While preclinical studies have provided encouraging results, further clinical research is essential to fully elucidate the mechanisms underlying saffron's antioxidant actions and validate its potential as a therapeutic agent for neurological disorders [297] .

4.3. Promoting Healthy Aging

Significant research focuses on identifying nutraceuticals that can prevent diseases, especially age-related diseases (ARDs), or mimic the anti-aging effects of drugs like metformin and rapamycin without side effects [298]. New candidates like allantoin, ginsenoside, and epigallocatechin gallate have shown promise and are undergoing experimental validation [298]. The intriguing idea that food-derived bioactive compounds could extend health span by modulating the senescence-associated secretory phenotype (SASP) opens up new strategies to delay the onset and progression of ARDs [299,300].

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While it is long known that nutrition influences health, the molecular pathways through which food impacts health still need to be fully understood [298]. Some bioactive compounds act as epigenetic modifiers, affecting gene expression, chromatin structure, DNA methylation, and non-coding RNA expression [301]. Studies have indicated that polyphenol-rich foods can modulate the activity of DNA writers and readers like DNA methyltransferases (DNMTs), histone deacetylases (HDACs), histone acetyltransferases (HATs), and HDAC SIRTs, highlighting a new mechanism that might contribute to healthy aging [302]. It is also suggested that certain compounds can influence the development and persistence of cellular senescence, with this epigenetic profile potentially being inherited by future cell generations [303].

Emerging evidence supports the ability of different phytochemical classes to modulate the senescence process, underscoring the importance of nutraceutical research for promoting healthy aging [303]. Data on the anti-aging effects of various natural and synthetic compounds are available in databases like Geroprotectors **(http://geroprotectors.org/resources)** and DrugAge **(https://ngdc.cncb.ac.cn/databasecommons/database/id/4466)**.

The scientific evaluation of the anti-aging effects of natural compounds is still in its early stages, and evidence regarding their senolytic properties is limited [298]. Tocotrienols, members of the vitamin E family, possess antioxidant properties and play roles in cell signaling, immune response, and apoptosis [304]. Recently, they have gained attention for their senolytic properties, stimulating senescence in cancer cells and reducing the accumulation of senescent cells in healthy tissues, thereby slowing the aging process [305]. Combining quercetin and dasatinib has significantly enhanced the health span in various mouse models [306]. Derived from Piper longum, Piperlongumine (PL) is known for its anticancer properties. It suppresses cancer stemness and has been shown to preferentially kill senescent human fibroblasts, making it a promising anticancer agent with potential senolytic effects [298].

5. Emerging Nutraceuticals and Future Directions

The field of nutraceuticals is rapidly evolving, with novel compounds and advanced technologies paving the way for more effective anti-aging interventions [21,197]. Novel compounds with potential anti-aging effects are at the forefront of current research [298]. For instance, pterostilbene, a compound structurally similar to resveratrol but with superior bioavailability, is gaining attention for its potent antioxidant and anti-inflammatory properties, which could play a crucial role in slowing the aging process and combating neurodegenerative diseases [307]. Similarly, urolithin A, a metabolite derived from ellagitannins found in pomegranates, has shown promise in enhancing mitochondrial function and promoting mitophagy, thereby supporting cellular health and longevity [308].

However, integrating nanotechnology in nutraceutical formulations is overcoming these barriers [309]. Nanoparticles, liposomes, and nanoemulsions are employed to encapsulate bioactive compounds, protecting them from degradation and improving their absorption and bioavailability [309,310]. For example, nano curcumin, a nanoparticle form of curcumin, has enhanced stability and bioavailability, leading to more pronounced anti-inflammatory and neuroprotective effects [249]. These cutting-edge delivery systems could revolutionize the effectiveness of nutraceutical interventions, making them more potent and reliable for preventing and managing age-related diseases [249,286].

Moreover, the future of nutraceuticals is moving toward personalized interventions tailored to an individual's genetic and epigenetic profile [311]. As our understanding of genomics and epigenetics deepens, it is becoming increasingly clear that the efficacy of nutraceuticals can vary significantly based on an individual's unique genetic makeup [311]. For instance, specific gene variants may influence how well a person metabolizes specific nutrients, impacting the effectiveness of nutraceuticals like omega-3 fatty acids or polyphenols [312]. By integrating genetic testing and epigenetic analysis, healthcare providers could tailor nutraceutical regimens to optimize their anti-aging effects [313]. This personalized approach could also involve monitoring epigenetic markers,

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such as DNA methylation patterns or microRNA expression, to adjust nutraceutical interventions dynamically, ensuring they remain effective as individuals age [313].

In summary, the future of nutraceuticals lies in developing novel bioactive compounds, applying advanced delivery technologies, and shifting toward personalized interventions based on genetic and epigenetic data [314]. These advancements promise to significantly enhance the role of nutraceuticals in promoting healthy aging and preventing age-related diseases, offering a more precise, effective, and individualized approach to health span extension [21,197].

6.0. Challenges and Limitations

While nutraceuticals hold great promise for promoting health and combating age-related diseases, several challenges and limitations must be addressed to realize their full potential [299,314]. A primary concern is the bioavailability and pharmacokinetics of nutraceuticals [315]. Many bioactive compounds in nutraceuticals, such as polyphenols, curcumin, and omega-3 fatty acids, have inherently low bioavailability due to poor absorption, rapid metabolism, and quick bodily elimination [315]. For example, despite its potent anti-inflammatory and antioxidant properties, curcumin is notorious for its poor bioavailability, as it is quickly metabolized in the liver and intestines [316]. This limitation severely reduces its effectiveness when consumed orally, leading to the need for higher doses or the development of advanced delivery systems, such as nanoparticles or liposomes, to enhance absorption and prolong circulation in the bloodstream [316].

Additionally, the pharmacokinetics of nutraceuticals, which involve their absorption, distribution, metabolism, and excretion, can vary widely among individuals due to age, genetics, gut microbiota composition, and overall health [317]. This variability complicates the standardization of dosing regimens and makes it challenging to predict therapeutic outcomes consistently [317]. Another significant issue is nutraceuticals' safety and long-term efficacy [317]. Although generally considered safe due to their natural origin, the long-term use of specific nutraceuticals may carry risks, particularly at high doses or in combination with other medications [317].

For instance, prolonged high-dose consumption of certain antioxidants like vitamin E has been associated with an increased risk of hemorrhagic stroke, highlighting the need for caution and proper dosage guidelines [318]. Moreover, the long-term efficacy of nutraceuticals remains an open question. While short-term studies often demonstrate beneficial effects, the robustness of clinical trials still needs to be improved to confirm that these benefits persist over years or decades of use [317]. The potential for cumulative side effects or interactions with other dietary supplements or medications over prolonged periods must be explored [317]. This gap in knowledge underscores the necessity for more extensive longitudinal studies to assess both the safety and sustained effectiveness of nutraceuticals in diverse populations [317].

Lastly, nutraceuticals' regulatory and ethical considerations present significant challenges [182]. The regulatory landscape for nutraceuticals varies considerably between countries, with some regions having stringent regulations similar to those for pharmaceuticals while others offer minimal oversight [182]. Nutraceuticals are often classified as dietary supplements rather than drugs, meaning they are not subject to the same rigorous testing for efficacy, safety, and quality [182]. This can lead to consistency in product quality, with variations in the concentration of active ingredients or the presence of contaminants. Furthermore, the marketing of nutraceuticals often includes claims not fully supported by scientific evidence, potentially misleading consumers about their health benefits [182]. Ethical concerns also arise from the commercialization of nutraceuticals, mainly when vulnerable populations are targeted with exaggerated promises of anti-aging or disease-preventive effects [182]. As the industry grows, there is a pressing need for more stringent regulations to ensure product safety, efficacy, accurate labeling, and ethical guidelines to govern the marketing and distribution of these products [182].

7.0. Conclusion:

This review highlights the critical role of nutraceuticals in addressing age-related conditions, focusing on PD and frailty. PD is a multifactorial pathology with non-motor symptoms that begins

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and is caused by inflammation and a reduction in neuronal capacity at least 20 years before (prodromal phase). The prodromal symptomatology is not easy to understand and is not always attributable to PD. In old age, we see a sum of dysfunctions; frailty mirrors many of the dysfunctional elements present in PD. It is still not well defined, so much so that geriatric frailty is spoken of as a multisite dysfunction coupled with aging.

In this scenario, nutriceuticals represent a way to guarantee an improvement in health at any stage of life, mainly when these dysfunctions manifest. Correct lifestyle, physical exercise, and diet are added to pharmacological therapies and prevention when dysfunctional pictures are not yet defined.

Nutraceuticals offer a promising avenue, targeting the underlying mechanisms of aging and neurodegeneration, such as oxidative stress, mitochondrial dysfunction, and inflammation. Despite the potential benefits, significant challenges remain, including bioavailability, long-term safety, and the need for robust regulatory frameworks. Advances in delivery systems and personalized approaches based on genetic and epigenetic profiles may pave the way for more effective and tailored nutraceutical interventions. However, nutraceuticals offer a promising avenue for addressing age-related conditions, mainly when used in conjunction with conventional therapies: their ability to target multiple biological pathways suggests that they may be able to enhance treatment outcomes and potentially reduce medication side effects.

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