FFHD
Functional Foods in Health and Disease

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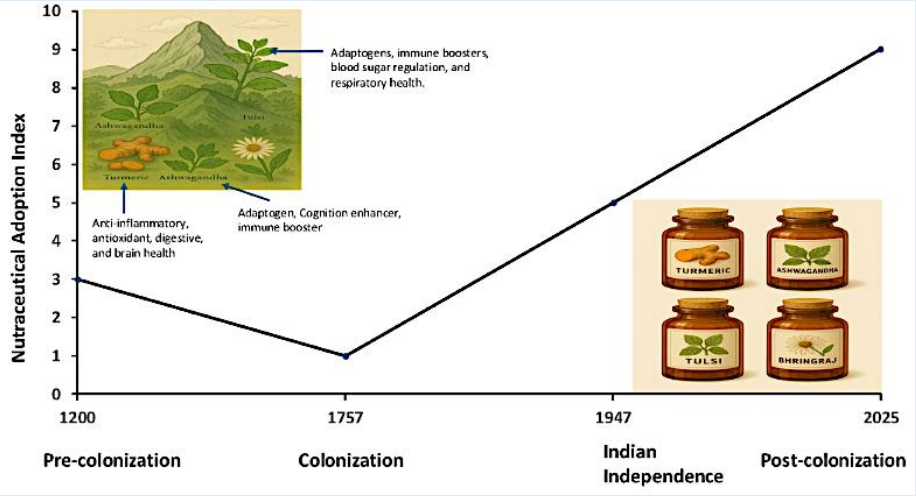
ABSTRACT

This review examines the historical evolution of the ancient Indian medical system, Ayurveda, through its precolonial, colonial, and postcolonial eras, along with its transformation into the modern framework of nutraceuticals. The article explores how Prakriti and the Tridosha Theory connect to genetic and epigenetic mechanisms, highlighting how doshic imbalances correlate with key molecular pathways involved in inflammation, metabolism, and stress regulation. Integrating traditional Ayurvedic perspectives with biomedical research supports Ayurveda as a promising foundation for advancing personalized healthcare and preventive medicine. During and after the COVID-19 pandemic, there has been a significant global shift toward natural, accessible health solutions. This led to substantial growth in the nutraceutical market. Nutraceuticals are bioactive compounds derived from foods and herbs that provide health benefits by acting as preventive or therapeutic agents in managing chronic diseases, including cardiovascular disorders, neurodegenerative conditions, and cancer. For example, nutraceuticals such as curcumin, resveratrol, and ashwagandha have been shown to modulate gene expression, influence cellular signaling pathways, and reduce oxidative stress, allowing them to enhance an individual's disease resilience. Ultimately, this review highlights the continued relevance of Ayurveda in the form of nutraceuticals, advancing holistic and integrative global health.

Key Words: Ayurveda, Tridosha, Prakriti, nutraceuticals, epigenetics, neurodegenerative diseases, preventative healthcare, metabolism, colonialism, stress, holistic medicine



Graphical Abstract: The Journey of Ayurvedic medicines to nutraceuticals

INTRODUCTION

Found in ancient texts such as the *Charaka Samhita* and *Sushruta Samhita,* which date back to more than 5,000 years, Ayurveda is one of the oldest systems of medicine. Rooted in the Vedic culture of India, Ayurveda has been a pillar for natural healing and holistic health. It focuses on maintaining balance between the body, mind, and environment through the use of herbs, diet, lifestyle adjustments, and natural therapies. In recent decades, Ayurvedic principles have gained renewed interest with the rise of nutraceuticals, which bridge the connection between food and medicine. Due to growing interest in alternative and integrative therapies beyond traditional Western medicine, Ayurveda's plant-based remedies are increasingly being examined for scientific validity, especially in fields like nutrigenomics and preventive medicine.

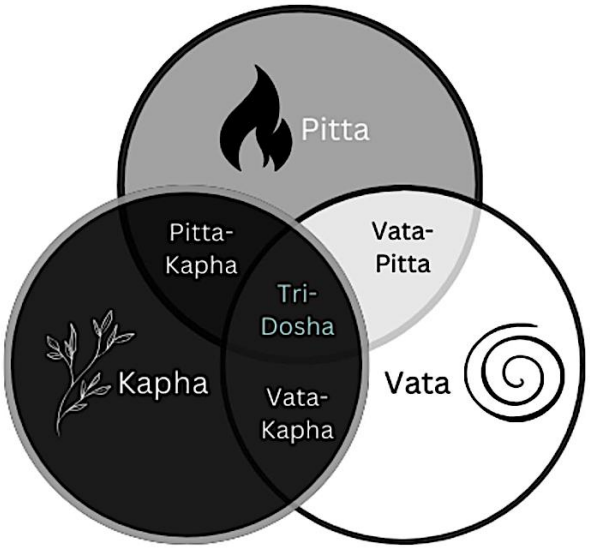
ORIGINS OF AYURVEDA

The Importance of Ayurveda and Its Use by Common People in Precolonial Times: The origin of Ayurveda dates to the Vedic period, approximately 1750 to 500 BCE (Figure 2), where it was practiced as a healing system. Its primary goal was to prevent diseases and promote holistic wellness by creating personalized treatments using natural remedies and lifestyle modifications that addressed the root causes of a given health issue [54]. The ancient practitioners recognized that the body's health depended on maintaining harmony with the environment: they linked disease to changes in the body's internal constitution (*Prakriti*) and its external surroundings [54]. For this reason, the concept of equilibrium is foundational in Ayurveda [54].

The *Charaka Samhita*, written by Charaka, an ancient Indian physician, and the *Sushruta Samhita*, written by Sushruta, an ancient Indian physician and surgeon, comprise the foundational texts of Ayurveda. The *Charaka Samhita* focuses on internal medicine, talking about *doshas* (body humors), *dhatus* (tissues), and *malas* (waste products) [40]. It promotes a holistic approach to diagnosis, therapy, and lifestyle modifications through herbal treatments, diet, and exercise [40]. The *Sushruta Samhita*, on the other hand, focuses on surgery. It provides anatomical studies, describes surgical methods, and details approximately 125 surgical instruments [35]. The *Ashtanga Hridaya* by

Vagbhata synthesized the knowledge of both Charak and Sushruta, presenting Ayurvedic concepts in poetic form, for easier memorization and transmission of information. It organized Ayurveda into a system with eight branches [42].

aI·ʎy' tKʎf2ă2LJKʎŜă 2Ŧ !èdzNØŜŘI·ππ¢NʎŘ2ăKI· ¢KŜ2NèY The Tridosha Theory in Ayurveda explains how the *Pancha Mahabhutas*, the five fundamental elements — earth (*Prithvi*), water (*Aap*), fire (*Teju*), air (*Vayu*), and space (*Akasha*) — combine to form three vital energies, known as *doshas*. The *doshas*, *Vata*, *Pitta*, and *Kapha*, maintain a dynamic balance. Together, the *doshas* are responsible for all physical, mental, and emotional functions in the body (Figure 1). Every individual has a unique combination of them, though one is typically dominant. Any imbalance in the *doshas* can increase a person's susceptibility to disease. Therefore, optimal health can be achieved by maintaining the balance of the *doshas* [58].



This diagram illustrates the foundational Ayurvedic concept of the Tridosha (Vata, Pitta, and Kapha).¶

CʎƎdzNŜ мY Overview of Ayurvedic Tridosha Theory

The *Vata* dosha, a combination of air and space, is responsible for all forms of movement within the body. This encompasses not only the physical movement of the limbs and the circulatory system, but also the flow of thoughts and emotions. Qualities such as dryness, lightness, coolness, subtlety, mobility, and irregularity are characteristic of *Vata*. *Vata*-dominant individuals are energetic, creative, and adaptable, with quick-thinking minds and lean, light body frames. However, their active state can make them prone to restlessness, anxiety, and overthinking. *Vata's* inherent irregularity also makes people with this constitution more likely to experience digestive issues, like constipation and bloating (Table 1). These people are also more sensitive to the cold and dryness, which can make them more susceptible to joint pain and insomnia. Therefore, *Vata* types need to incorporate warmth, nourishment, and stability in their daily routines to maintain inner balance. An ideal diet for *Vata*-dominant individuals includes warm, cooked, and easily digestible foods, such as soups, stews, and whole grains prepared with healthy fats like ghee (Table 1). This diet combats the dryness to which *Vata* individuals are

prone. Similarly, therapies such as *Abhyanga* (oil massage) with warm oils help to soothe and ground the *Vata* constitution [9]. Additionally, establishing a stable, calming routine, including regular sleep cycles, yoga, and meditation, can help promote the equilibrium and balance that Ayurveda emphasizes.

On a cellular level, *Vata* plays a vital role in the signaling pathways that govern cell growth, differentiation, and death. An example is the regulation of the Akt/mTOR pathway, which is involved in cell growth and survival [24]. It manages fatty acid metabolism, amino acid synthesis, and neurotransmitter levels for various compounds, including dopamine, glutamate, and lysophospholipids (Table 1). *Vata* types are susceptible to imbalances in this pathway, which can lead to neurological disorders, insulin resistance, and inflammatory responses due to disruptions in secondary lipid signaling and metabolic processes [60].

The *Pitta* dosha, which is made of fire and water, governs metabolism, digestion, nutrient absorption, and body temperature. It also plays a key role in a person's intelligence and cognitive ability. *Pitta's* primary qualities include heat, sharpness, intensity, lightness, and liquidity. Individuals with a dominant *Pitta* usually have medium builds, warm complexions, strong digestive fire (*Agni*), and sharp, focused minds. They are generally competitive and ambitious, which can be a strength, but it also makes them more prone to irritability and impatience [20]. Because of *Pitta's* fiery nature, when *Pitta* becomes aggravated, a person may experience physical symptoms such as excessive sweating, inflammation, especially in the form of skin rashes, acid reflux, and ulcers. Emotionally, aggravated Pitta individuals may experience heightened anger, frustration, and a tendency toward perfectionism. To stay balanced, *Pitta* types benefit from calming, grounding practices (Table 1). Engaging in relaxing activities, like yoga with a focus on the spine, or massage and skincare with coconut and sandalwood-based products, can help soothe an aggravated *Pitta* [18]. Their ideal diet includes sweet, bitter, and astringent foods like fresh fruits, leafy greens, and cooling beverages. It's also recommended to avoid spicy, oily, and salty foods, which can increase their *Agni*. By adopting a more mindful, calming, and grounding lifestyle, along with maintaining a balanced diet, individuals with a *Pitta*-dominant constitution can preserve harmony and health [9].

On the cellular level, *Pitta* is linked to the regulation of hormonal balance, energy production, and enzymatic reactions, thereby ensuring optimal physiological function in an individual. For example, *Pitta* influences key hormones, like cortisol for stress, insulin and 2-methoxyestrone for metabolism, melatonin for the circadian rhythm, and reproductive hormones (Table 1) [24]. In terms of energy production, *Pitta* can be thought of as the body's internal fire, which helps generate the energy, ATP, that the body needs to function. As for enzymatic reactions, Pitta regulates those involved in digestion and metabolism, such as amylase, protease, and lipase. Metabolism of toxins and xenobiotics occurs through cytochrome P450, but in *Pitta*-dominant constitutions, there are often issues with beta-oxidation due to higher lipid absorption and elevated bile acids. These factors contribute to *Pitta's* fast metabolism and active physical state [55].

Finally, the *Kapha* dosha is derived from the elements of earth and water, representing stability, structure, and cohesion within the body's processes. It governs growth, immunity, and lubrication. Its primary qualities are heaviness, slowness, coolness, smoothness, and steadiness. *Kapha*-dominant individuals are calm, nurturing, and grounded, often having physically sturdy builds, smooth skin, and strong immunity (Table 1). They are resilient and patient, but may be more prone to lethargy and attachment. When the *Kapha* dosha becomes excessive, it can lead to weight gain, congestion, lethargy, and psychological issues such as

emotional resistance and depression [20]. To prevent heaviness and stagnation, *Kapha*-dominant individuals thrive on stimulation and movement. Their ideal diets focus on light, warm, and spicy foods, while avoiding heavy, oily, and sugary items [18]. Incorporating vigorous activities like running or dancing into their daily routines can help maintain a lively, stimulating environment. Therapies such as dry brushing and massage, which promote circulation, are also very beneficial (Table 1).

At the cellular level, *Kapha* is involved in synthesizing the extracellular matrix, collagen, and bone density. Additionally, it is responsible for maintaining the functionality of all connective tissues [24]. It also regulates phagocytosis, antibody production, and cytokine signaling in the immune system (Table 1). More, *Kapha* aids in maintaining fluid homeostasis, including electrolyte balance and osmotic pressure. *Kapha* also supports lipid metabolism by regulating cholesterol levels and the formation of adipose tissue. An imbalance in *Kapha* can cause fluid retention, diabetes, and respiratory issues, like asthma. A deficiency may weaken immunity and cause brittle bones or joint instability [24].

¢l-ōŀŜ м: Scientific Explanations of Tridoshas.

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Vata	Air, Space	Governs movement, breathing, nerve impulses, and thoughts [58]; traits include creativity, adaptability, quick thinking, and lean build [9]	Anxiety, overthinking, insomnia, joint pain, constipation, bloating [9]	Warm, moist, nourishing foods like soups and stews, healthy fats (ghee), regular routines, yoga, meditation, and oil massage (Abhyanga) [9]	Regulates Akt/mTOR pathway involved in cell growth and survival [24]; controls neurotransmitter levels (dopamine, glutamate, lysophospholipids) and fatty acid metabolism [60]; imbalances linked to neurological disorders, insulin resistance, and inflammation [60]
Pitta	Fire, Water	Controls digestion, metabolism, temperature regulation, and intellect [58]; traits include medium build, strong digestion, warm complexion, and ambition [20]	Irritability, inflammation, ulcers, acid reflux, skin rashes, excessive sweating [20]	Cooling foods (leafy greens, fruits), calming routines, coconut oil massages, avoiding spicy/oily/salty food, and yoga [9], [17]	Linked to ATP production via the electron transport chain [24]; regulates digestive enzymes (amylase, lipase, protease) [24]; affects hormones like cortisol, insulin, melatonin, 2-methoxyestrone [24]; involved in cytochrome P450 metabolism and lipid absorption [55]
Kapha	Earth, Water	Provides stability, structure, immunity, and lubrication [58]; traits include calmness, groundedness, nurturing nature, and strong build [20]	Lethargy, weight gain, congestion, depression, emotional resistance or attachment [20]	Light, warm, spicy foods; vigorous exercise (e.g., running, dancing); dry brushing; circulation-promoting massages [18]	Supports collagen synthesis, extracellular matrix formation, bone density, and connective tissue health [24]; regulates immune function (phagocytosis, antibodies, cytokines), fluid homeostasis (electrolytes, osmotic pressure), and lipid metabolism (cholesterol, adipose tissue) [24]

Table 1. This table outlines the elemental composition, primary functions, and typical personality traits of the *Vata*, *Pitta*, and *Kapha doshas*, common imbalances, their corresponding Ayurvedic remedies, lifestyle recommendations, and the cellular and biochemical pathways associated with each.

tŊl-ƪŊʎŭʎππ!y hǿŜŊǿʎŜǿY Everyone is born with a unique *Prakriti*, or constitution, that determines their inherent balance of the *doshas*. According to Ayurveda, this balance is influenced by both genetic and environmental factors, especially during conception and the early stages of development. Factors such as the mother's eating habits during pregnancy, the parents' age (*Kala Garbhashaya*), ethnicity (*Jati*), familial characteristics

(*Satmya*), and the region where the individual belongs (*Desha*) can all impact the development of *Prakriti* [46]. Over time, external influences such as diet, stress, and specific environmental exposures can disrupt the balance of the *doshas*, creating imbalance or disease (*Vikriti*). This disruption is linked to health conditions that range from metabolic disorders to cardiovascular and neurological diseases [54].

***Prakriti* ꟹ aŜűl-ō2ťľăYʏ** The concept of *Prakriti* is deeply intertwined with metabolism, as each dosha is traditionally associated with specific metabolic tendencies. *Vata*, which governs movement and energy flow, is linked to variable metabolism. *Pitta*, responsible for digestion, heat, and transformation, corresponds to a faster metabolic rate. *Kapha*, associated with structure and stability, is typically linked to slower metabolism. These metabolic tendencies influence an individual's response to diet, exercise, and environmental factors.

Several studies have explored the effect of *Prakriti* on metabolic processes. For example, research indicates that individuals with a *Vata-Pitta* constitution tend to have a lower body mass index (BMI) than those with a *Kapha-Pitta* constitution [14]. Additionally, metabolic disorders such as obesity, hypertension, and diabetes are more common in people with *Kapha* dominance. *Kapha* types also often exhibit elevated lipid profiles, including low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and triglycerides, which reflects a greater propensity for lipid storage and chronic inflammation [14]. Meanwhile, *Pitta* types may have tissue wear and early aging due to faster metabolic rates [14]. *Vata* types are known for their vulnerability to neurological conditions due to their fluctuating metabolism. These variations in metabolic activity match Ayurvedic classifications and open new possibilities for personalized health strategies based on metabolic type.

One of the most extensively studied genes in this context is CYP2C19, which encodes a cytochrome P450 enzyme involved in the hepatic metabolism of drugs. Individuals with a *Pitta*-dominant *Prakriti* often exhibit the extensive metabolizer genotype, correlating with a faster metabolic rate. In contrast, *Kapha* individuals are more likely to have the poor metabolizer genotype, reflecting their slower basal metabolic rate (BMR). In addition, HLA allele variations have been linked to different *Prakriti* types, indicating innate differences in immune regulation and susceptibility to immune-mediated diseases.

Another key gene is EGLN1, which plays a role in hypoxia response and energy metabolism. *Kapha* individuals have been found to have a higher frequency of the TT genotype of EGLN1. This gene encodes a protein involved in regulating the hypoxia-inducible factor pathway, a pathway responsible for the body's response to low oxygen levels. This may predispose them to oxidative stress and pulmonary complications under metabolic strain [14]. Conversely, *Pitta* types, with a lower frequency of this variant, appear more resilient to oxidative stress. While *Pitta* types exhibit increased expression of genes related to oxidative stress [14], gene expression studies reveal that individuals with *Vata*-dominant *Prakriti* express higher levels of inflammation markers in the body, such as IL-6 and TNF-α.

Hormonal and nuclear receptor genes also appear to contribute to *Prakriti* distinctions. *Pitta* types may be influenced by the enhanced activity of androgen receptors (AR), which supports their mesomorphic build and high BMR. Thyroid hormone receptors are potentially more active in *Vata* types, aligning with their fluctuating energy levels and nervous system sensitivity. *Kapha* individuals, with their stable and robust constitution, may be modulated by thymus-related

immune factors, suggesting a genetically reinforced immune tolerance. Additionally, hematologic gene expression differs between the Tridosha, with *Pitta* exhibiting higher expression of hemoglobin-related genes, thereby enhancing oxygen transport, and *Vata* showing variability in platelet aggregation and coagulation factors. Together, these genetic and molecular patterns support the traditional Ayurvedic view of individualized metabolic function based on *Prakriti* and may provide biomarkers for personalized medicine [14].

tNJl·ʅNJʎúʎ ϑ 9LJʎƎŜyŜúʎŎăY Epigenetics is the study of modifications to gene expression that occur without changing the underlying DNA sequence. These changes are usually triggered by external factors, such as diet, toxins, stress, and lifestyle, which can turn specific genes on or off. This, in turn, affects cell function and metabolism, leading to disease susceptibility. The main mechanisms of epigenetics include DNA methylation, histone modification, and RNA-mediated regulation [46,54]. DNA methylation involves adding methyl groups to DNA, which can suppress gene activity. Histone modifications change how accessible DNA is for transcription, typically by making genes open. RNA-mediated regulation through microRNAs (miRNAs) can block protein production by silencing certain messenger RNAs (mRNAs) and stopping translation. All epigenetic modifications are reversible, which means therapeutic interventions can be made.

The concept of *Prakriti* in Ayurveda has numerous parallels with modern epigenetics. Modern research has shown that genetic predispositions, combined with environmental and lifestyle inputs, influence gene expression and health outcomes, which closely mirrors the Ayurvedic principle of dosha balance and *Vikriti* [54]. Researchers have drawn parallels between the three *doshas* and molecular biology: *Vata*, which is associated with movement, aligns with messenger RNA (mRNA), which transmits genetic information for protein synthesis. *Vata*'s mobile nature is akin to the role of mRNA in regulating cellular communication and energy flow. *Pitta*, which is responsible for transformation and metabolism, corresponds to transfer RNA (tRNA), which assembles amino acids into proteins. *Pitta*'s qualities parallel the metabolic and enzymatic processes mediated by tRNA. *Kapha*, which represents stability and structure, mirrors the process of protein synthesis, which builds and maintains bodily tissues. *Kapha*'s structural characteristics align with the foundational role of proteins in cellular stability [54]. These associations suggest that Ayurveda can be aligned with a biochemical foundation, highlighting how lifestyle, diet, and mental health can influence gene expression through epigenetic mechanisms [46].

The interaction between *Prakriti* and epigenetics highlights Ayurveda's potential in preventing disease through a balanced diet tailored to an individual's *Prakriti*. For example, foods rich in polyphenols, such as turmeric, green tea, and pomegranate, have been shown to influence gene expression related to inflammation and cancer prevention via epigenetic mechanisms. Turmeric's active compound, curcumin, a polyphenol, inhibits histone deacetylases, which helps suppress tumor growth and promote healthy gene expression [46]. Herbs can also modulate epigenetic pathways. One example is Withaferin A, a compound found in Ashwagandha, which has been shown to downregulate DNA methyltransferases and histone deacetylases, promoting apoptosis in cancer cells and supporting cellular health by preventing tumor growth [46].

Chronic stress is known to induce epigenetic

changes, such as hypermethylation of stress-response genes, which then lead to heightened inflammation and increased disease risk. Ayurvedic practices, such as meditation and yoga, can reduce stress levels and potentially reverse these epigenetic changes. Research has shown that stress reduction techniques can upregulate protective genes and downregulate pro-inflammatory pathways, which aligns with Ayurveda's emphasis on psychological and physiological balance [54].

Exposure to environmental toxins, such as air pollution or heavy metals, can also disrupt gene expression through epigenetic mechanisms. Ayurveda's detoxification practices, including Panchakarma, aim to eliminate toxins and restore doshic balance, potentially reversing harmful epigenetic modifications. Studies suggest that such interventions may enhance the body's ability to repair DNA and maintain cellular homeostasis [46].

Ayurveda's emphasis on reversing imbalance (*Vikriti*) through diet, lifestyle, and herbal remedies is mirrored by the reversibility of epigenetic changes. Just as Ayurvedic therapies aim to realign the *doshas*, modern science demonstrates that environmental and lifestyle modifications can reverse unfavorable epigenetic changes. This relationship between *Prakriti* and epigenetics offers a compelling framework for integrating ancient wisdom and modern science in the medical field, highlighting the potential of Ayurveda in advancing preventive healthcare and personalized medicine by offering pathways to optimize health, prevent disease, and reverse imbalances at the genetic and molecular levels [46,54].

¢KŜ CλǾŜ /I-ǘŜƎƻNJλŜă ƻŦ IŜNJōăY In Ayurveda, there are five categories of herbs: *Rasa* (taste), *Veerya* (potency or energy), *Vipaka* (post-digestive effect), *Prabhava* (unique action), and *Karma* (therapeutic action). These classifications each affect how certain herbs interact with the body and influence the *doshas*ΦDetected

Rasa is divided into six categories: *Madhura* (sweet), *Amal* (sour), *Lavana* (salty), *Katyayavya* (pungent), and *Kashaya* (astringent). It refers to the taste immediately perceived when the tongue encounters an herb [41]. These flavors influence dosha balance because they are also a combination of the five elements. For instance, *Madhura* consists of water and earth, aggravates *Kapha* but soothes *Pitta* and *Vata*.

Veerya is the energy produced by an herb during digestion. It is divided into *Sheeta* (cooling) and *Ushna* (heating). Cooling herbs, such as sandalwood, reduce inflammation and an aggravated *Pitta*, while hot herbs, like turmeric, lessen *Kapha* stagnation. These herbs also improve digestion and circulation.

Vipaka determines the herbs' long-term effects after digestion and is categorized into three types: *Madhura* (sweet), *Amla* (sour), and *Katu* (pungent). *Madhura Vipaka* nourishes the body, builds strength, enhances immunity, and supports reproductive health. It calms *Vata* and *Pitta* but can increase *Kapha* when consumed in excess, leading to weight gain and sluggishness. An example is the *Vipaka* of licorice (*Glycyrrhiza glabra*), categorized as *Madhura*, which decreases inflammation and nourishes tissues [41]. *Amla Vipaka* improves digestion, boosts appetite, and enhances nutrient absorption. Long-term use increases *Pitta* and *Kapha*, which may cause acidity, inflammation, and irritability. *Katu Vipaka* stimulates metabolism, reduces fat, and clears congestion. It lowers *Kapha* but raises *Vata*, and over time, can cause dryness, anxiety, and weakened reproductive health.

Prabahva describes an herb's unique, usually inexplicable function that goes beyond its general characteristics. For example, Ashwagandha is an adaptogenic herb that increases stress tolerance, while Guggulu promotes lipid metabolism.

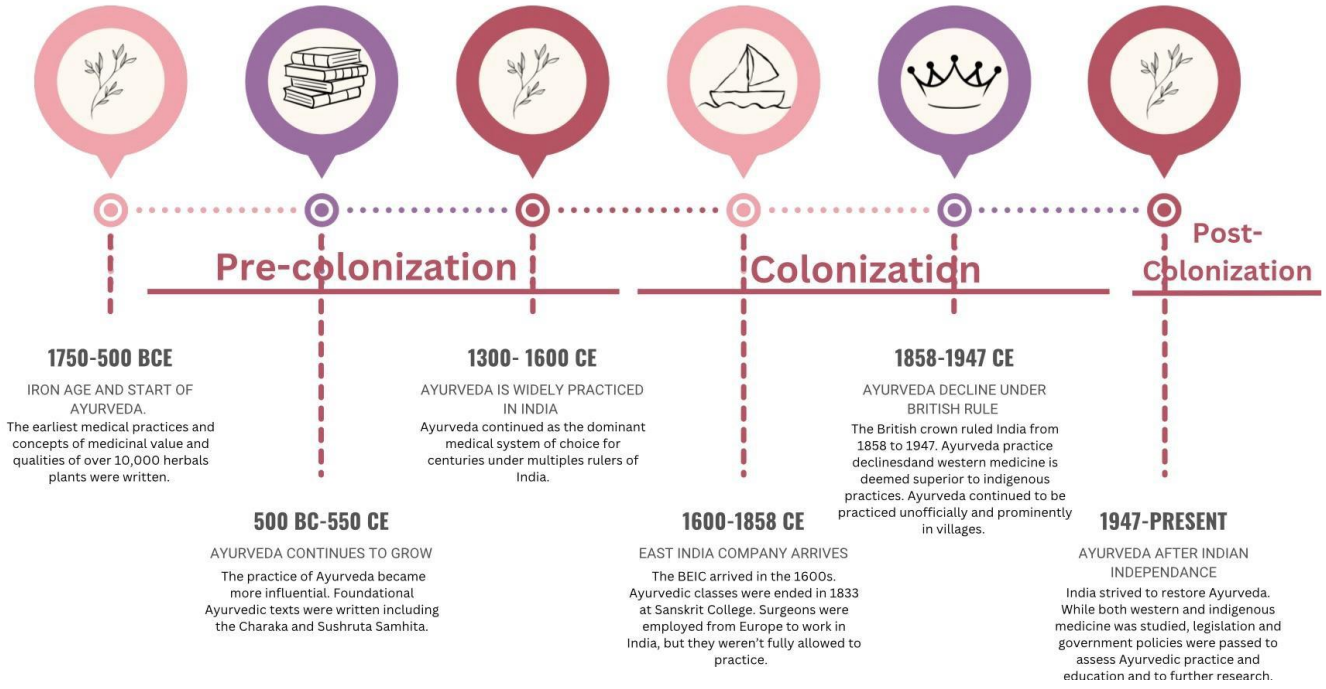
Karma describes an herb's medicinal properties in addressing specific conditions: *Anuloman* (carminative), *Virechana* (laxative), *Shodhana* (detoxifying), *Pachana* (digestive aid), and *Deepana* (digestive stimulant) [41]. Ginger is an example of *Deepana* and *Pachana*, as it helps alleviate digestive issues such as bloating.

By being aware of these herbal classifications, practitioners can further integrate Ayurveda's holistic healing approach by tailoring treatments according to each patient's doshic constitution.

Pathaya* Ó& *ApathayaЎ *Pathaya* and *Apathaya* are fundamental concepts in Ayurveda, categorizing food as a form of medicine that can promote well-being or lead to imbalances in the *doshas*. These classifications also account for factors like preparation methods, seasonality, and an individual's constitution [36]. *Pathaya* consists of wholesome, beneficial, and easily digestible foods that allow the body to maintain equilibrium. In contrast, *Apathaya* consists of foods and habits that disrupt the body's harmony, therefore leading to disease and discomfort. These classifications are not dependent on the food alone, but rather on factors like preparation methods, seasonality, and an individual's constitution [36]

Pathaya consists of wholesome, nutritious, and easily digestible foods that allow the body to maintain equilibrium. Many traditional Ayurvedic recipes are designed to be gentle on the digestion. For instance, khichdi and warm water infused with spices like cinnamon and coriander are considered *Pathaya* as they aid digestion and metabolism [49]. Additionally, season plays a crucial role in determining whether a food is *Pathaya*. To help regulate body temperature, *Pathaya* foods counteract the environmental temperature. So, during the winter, warm foods like ginger and garlic are recommended, while cooling foods like fresh fruits, cucumbers, and green squash are recommended in the summer. *Pathaya* foods are also prepared in a way that changes their properties to make them more suitable for an individual's *Prakriti*. For example, buttermilk, which is made by churning curd and removing the butter, is considered *Pathaya*. Curd is heavy, sour, and cooling, which can aggravate the *Kapha* dosha. However, if the curd is churned and the butter is removed to produce buttermilk, it becomes *Pathaya* for a *Kapha*-dominant individual. This is because buttermilk is lighter and easier to digest, making it beneficial for conditions like irritable bowel syndrome, hyperacidity, fissures, and diarrhea [46]. Beyond diet, healthy mealtime habits, like eating fresh, balanced meals at regular intervals with a calm, happy state of mind, are also characteristic of Pathaya.

In contrast, *Apathaya* foods disrupt the body's equilibrium, impair digestion, and make individuals more vulnerable to diseases. Excessive consumption of specific tastes, for example, can aggravate *doshas* and lead to health issues. Consuming too much salty and sour food can elevate the *Pitta* dosha, resulting in acid reflux, inflammation, and hypertension. Similarly, an excessive consumption of sweets can increase the *Kapha* dosha, leading to weight gain, lethargy, and mucus-related disorders. The seasons also influence *Apathaya*. For instance, during the winter, consuming cold, light, and dry foods can aggravate *Vata*, which may cause joint pain, dry skin, and digestive problems. During the summer, warm and pungent foods can exacerbate *Pitta*, increasing body heat and leading to excessive sweating and rashes [49]. *Apathaya* lifestyle practices, such as overeating, eating irregularly, and eating under stress, further disrupt digestion and contribute to imbalance and illness.



CłƎdzŇŜ н◊ Timeline of Ayurveda: From ancient roots to modern use. This timeline traces the development of Ayurveda from its origins in ancient India and foundational classical texts, through periods of decline during colonization, to its revival and growing global recognition in modern wellness and medicine.

Ayurveda also provides specific guidelines for *Pathaya* and *Apathaya* in managing illnesses. For instance, when an individual has a fever (*Jvara*), light foods like rice porridge (*Yavagu*) and warm herbal decoctions are recommended to promote revival and recuperation. In contrast, heavy and oily foods are considered *Apathaya*, as they strain the digestive system. For metabolic diseases, like diabetes (*Prameha*), old barley and green gram soups are considered *Pathaya*, whereas excessive consumption of sugar, dairy, and refined carbohydrates is *Apathaya*. *Pathaya* foods for skin disorders (*Kustha*) are bitter-tasting vegetables and ghee with *triphala* and honey, while sour, spicy, and fermented foods are *Apathaya* because they can exacerbate inflammation [36].

!ѐdzŇØŜŘĬ· I·ă I· {ѐăűŜY' Ayurveda is traditionally divided into eight branches, each addressing different aspects of health. The first branch is *Kaya Chikitsa*, or Internal Medicine, focusing on treating systemic disorders of both the mind and body, including digestive health, metabolic disorders, and chronic illnesses. The second branch is *Shalakya Tantra*, which specializes in diseases affecting the organs above the clavicle, such as the eyes, ears, nose, and throat. The third branch, *Shalya Tantra*, is a form of surgery. It involves procedures that remove foreign bodies, treat wounds, and perform cauterization [17,26]. The fourth branch is *Agada Tantra*, encompassing toxicology. It deals with poisons from animals, plants, and minerals, along with their antidotes and detoxification methods. The fifth branch, *Bhuta Vidhya*, addresses psychiatric disorders using herbal therapies, medications, and rituals. The sixth branch, *Kaumarabhritya*, focuses on neonatal and child health, emphasizing nutrition, immunity-boosting therapies, and disease prevention [17,26].

The seventh branch is *Rasayana Tantra*, which encompasses geriatrics and rejuvenation, promoting longevity, improving cognitive function, and maintaining

youthfulness through special diets, herbal medications, and rejuvenation therapies. The final branch is *Vajikarana Tantra*. It focuses on enhancing reproductive health, fertility, and improving vitality by implementing specific diets, herbs, and lifestyle practices. These eight branches together form Ayurveda's medical system, which not only treats diseases but also emphasizes disease prevention and overall holistic health [17,26].

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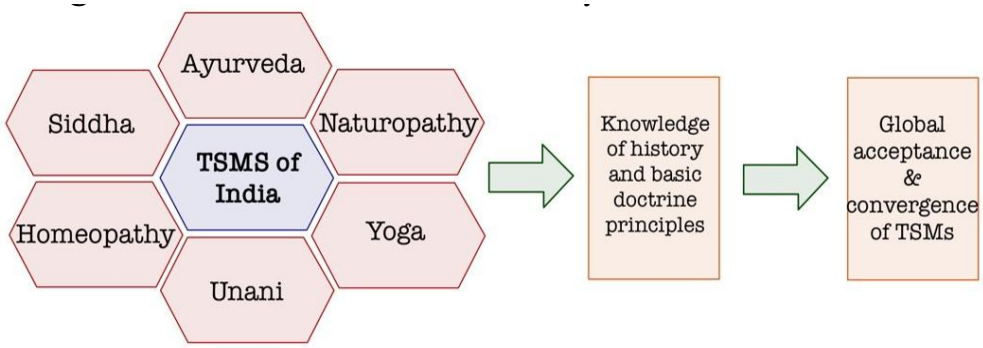
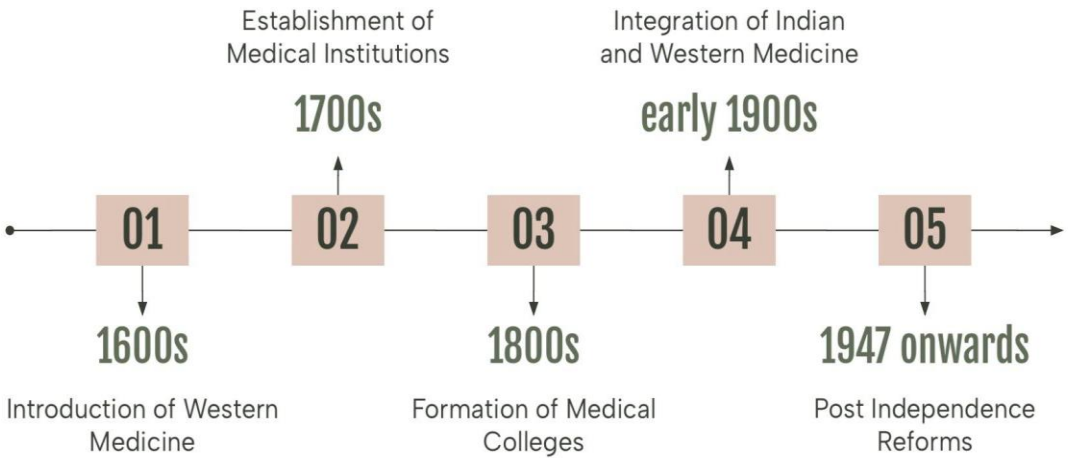
.ₓλúλăK tŜₓŎŜLJúλ2y 2₮ !èdzₓØŜŘI·Y The British arrival in India in the early 1600s led to a significant transformation in the perception and practice of Ayurveda. British medical practitioners initially showed some interest in Ayurveda, acknowledging its extensive botanical and pharmacological knowledge. However, as colonial rule became increasingly expansive, British administrators began to dismiss Ayurveda, considering it outdated and unscientific. They believed their Western medicine, the allopathic medical system, was superior. This Eurocentric perspective led to the systematic marginalization of Ayurveda, which significantly altered the entirety of India's medical practices [4, 38]. By the late 19th century, Ayurveda faced a significant decline (Figure 2) as an academic and professional field of medicine [4].



CλΞdzₓŜ o¢ Traditional medical systems of India. This figure shows how India's traditional medicinal systems like Ayurveda, Siddha, and Unani were once practiced separately, but gradually began to overlap and converge as they gained recognition and acceptance around the world.



CλΞdzₓŜ n¢ Timeline of Ayurvedic education through the centuries. Figure 4. This timeline shows how Ayurvedic education changed over time by noting the introduction of Western medicine and the integration of medical schools that taught Western medicine during colonization, and later the rise of Ayurvedic education through national movements and modern institutions that helped bring Ayurveda back into academic and clinical practice.

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{KʎŦű ¢2ǿI-ŊŘǎ !ff2LJI-űKè ʎy 9ŘdzŎI-űʎ2yY In 1822, the Native Medical Institution was founded in Calcutta, allowing 20 Indian students to learn both Western and Ayurvedic medicine in their native languages. By 1826, the Sanskrit College of Calcutta offered Ayurvedic courses, and graduates from these schools were given government jobs.

However, Thomas Macaulay, a British politician and historian, who is a significant figure in making English the medium of instruction for higher education in India, believed that Indian medical students should receive an education in English rather than their native language. As a result, Calcutta Medical College was established, modeled after European standards (Figure 4). Forty-nine students, between the ages of 14 and 20, were trained for four to six years in Western medicine practices. Upon completion of coursework, students were eligible to sit for an exam that allowed them to become certified in internal medicine and surgery [4].

In 1835, the British abolished the Native Medical Institution and discontinued classes in Ayurvedic medicine at prominent institutions. If Ayurvedic scholars and practitioners were to operate, they were expected to do so independently, with government support. This caused the divide between Western and indigenous medical systems to widen. As British colonial rule endured, Ayurvedic medicine received significant institutional and financial backing. At the same time, Ayurveda became a practice relegated to rural areas and passed down through family lineages rather than educational institutions. [4]

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wŜǿʎǿI-ƚ 2Ť !èdzŊǿŜŘI· !ŦűŜŊ LyŘŜLJŜyŘŜyŏŜ ŦŊ2Y űKŜ .ŊʎűʎǎKY India gained its independence from the United Kingdom in 1947. Post-independence, efforts were made to revive and reintegrate Ayurveda into the national healthcare system. Nationalist leaders, such as Mahatma Gandhi and Pandit Nehru, recognized the significance of Ayurveda both culturally and medically, advocating for its restoration alongside modern medicine rather than eradicating allopathic medicine (Figure 4). As part of this movement, Ayurvedic institutions were reestablished, and government initiatives were introduced to regulate and promote traditional medicine [38]. In 1995, the Indian government took a significant step by establishing the Department of Indian Systems of Medicine and Homeopathy, later renamed the Ayurveda, Yoga & Naturopathy, Unani, Siddha, and Homeopathy Ministry (AYUSH) in 2003 (Figure 3). The principle behind Homeopathy is the idea of "Like cures like", which states that a substance that causes symptoms in a generally healthy person can be used in tiny doses to treat similar symptoms in a sick person [39]. In a study conducted, it was observed that homeopathic remedies, such as *Cobaltum* and *Causticum*, reduced the severity of radiotherapy-related side effects, with a lower reaction

index in the treatment groups compared to the placebo. The goal of AYUSH was to standardize Ayurvedic education, regulate the medicinal quality of Ayurvedic practice, and, above all, support research for Ayurveda (Figure 4). However, despite these efforts, Ayurveda continues struggling to achieve the same credibility and funding as allopathic medicine. To date, Western medicine continues to dominate Indian public healthcare and medical education [4, 38].

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5ŜŦʎƴʎƴƎ bdzúNI·ŎŜdzúʎŎI·fãƴ Nutraceuticals are compounds derived from natural or processed foods that are specifically meant for prophylactic or therapeutic purposes. Put, they are intended to prevent and treat disease. These substances are categorized as neither food nor drug; instead, they are formed by combining the words “nutrient” and “pharmaceutical” to signify their role as both [44].

Nutraceuticals are often grouped with other health-related products, such as dietary supplements or functional foods, but it's essential to understand the differences between the three. Nutritional supplements are substances, such as vitamins, minerals, and herbal extracts, that enhance health by providing the body with essential nutrients. However, they are not designed to prevent or treat diseases. Functional foods include natural or processed foods enhanced by biologically active compounds. Examples include probiotics or omega-3 enriched eggs, which offer benefits beyond the basic nutrition an individual needs. Like dietary supplements, functional foods are not intended as preventative treatments [10]. When either is used for the prevention and/or treatment of diseases or disorders, they become nutraceuticals [53].

Nutraceuticals offer certain benefits over conventional allopathic medicine. For example, while modern drugs treat symptoms, they often cause significant side effects or dependency risks. Nutraceuticals come from natural sources and typically have minimal or no adverse effects. They are often more affordable and accessible than prescription drugs since they are available over the counter and do not require a prescription. Their safety, convenience, and holistic benefits make them a good alternative for improving health and preventing chronic conditions [44].

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Nutraceuticals have gained increasing prevalence as consumers have shifted towards preventive healthcare. In recent years, global demographics have shifted towards an aging population, and older individuals are trying to find protection against stress and age-related conditions. These conditions include Alzheimer’s disease, dementia, respiratory disorders, hypertension, CVD, osteoporosis, and cataracts. Nutraceuticals have effectively reduced the incidence of degenerative diseases, promoted longevity, and improved overall well-being in older individuals. This makes them a vital tool and an essential advancement in extending (health span) in aging populations worldwide.

A significant increase in consumer demand for natural, preventative wellness products was also marked by the COVID-19 pandemic [11]. This trend became especially pronounced in regions such as the United States, Canada, and Asia-Pacific, where multiple factors, including rising disposable income, urbanization, and the higher prevalence of lifestyle-related diseases like hypertension and diabetes, caused an increase in demand for nutraceuticals. Rising healthcare and prescription drug costs also allowed for a push towards nutraceutical products as consumers looked to find cost-effective alternatives.

Moreover, various distribution channels, including online sales, direct marketing, and specialized retail stores, have created accessibility and increased sales. The convenience of e-commerce and a growing internet-savvy population have made online shopping for

nutraceuticals particularly popular. Companies utilize digital marketing, social media, and other innovative strategies to reach broader audiences effectively. Nutraceuticals represent a promising avenue for enhancing health, addressing chronic conditions, and providing affordable, preventive healthcare solutions for a diverse and increasingly health-conscious global population [11].

/dzNNuŜyú Df2ōl·f aI·MJ]ŜúY North America is the largest nutraceutical market, driven by high disposable incomes, a strong wellness culture, and continuous innovation in product development. The United States alone accounted for a significant portion of global revenue, with a predicted market projection that estimated a growth of a CAGR of 5.5% to 6.0% (Figure 5) between 2016 and 2022, reaching over $95 billion in value during that period [11]. Key factors driving this growth include the popularity of immune-boosting supplements, protein powders, and functional beverages, like yogurt drinks or vitamin-infused water. Products such as omega-3 fatty acids, probiotics, and collagen-based supplements are also in particularly high demand due to their perceived benefits for cardiovascular health, digestion, and skin care. Canada also plays a substantial role in the development of the nutraceutical market. It contributed over $11 billion in revenue from its functional foods and natural health products sector as of 2011, with consistent growth projected at 5.62% CAGR from 2019 to 2024. The country has over 32,000 natural health products on the market, emphasizing its commitment to nutraceutical innovation.

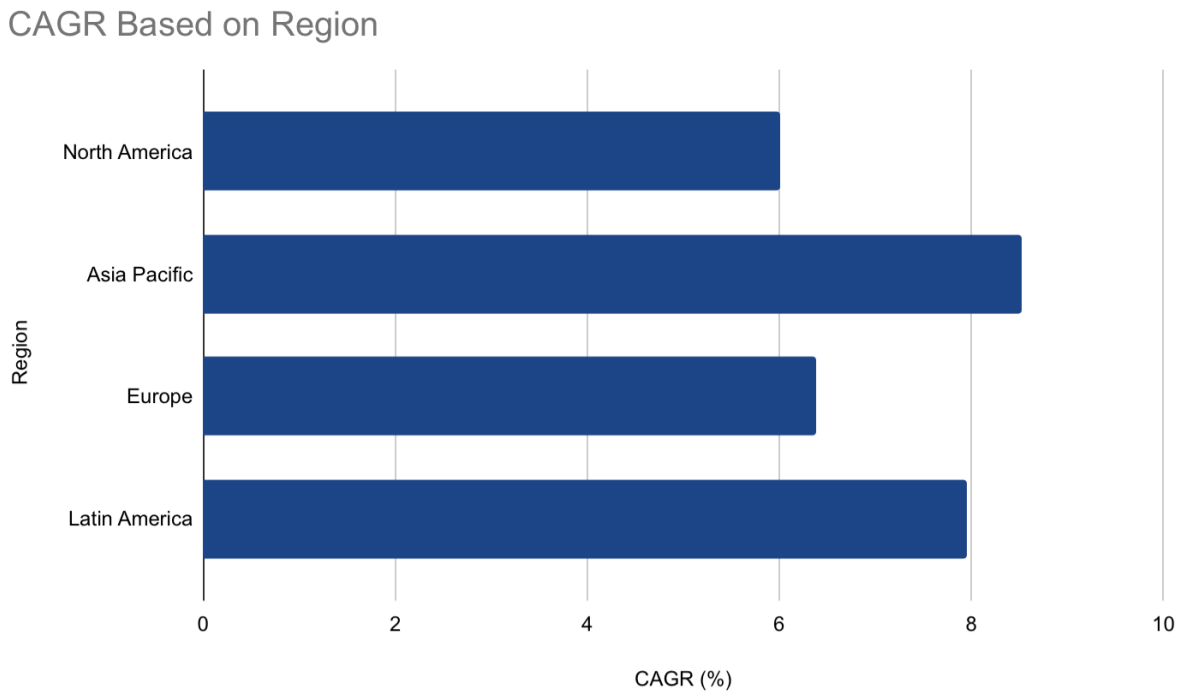
The Asia-Pacific region is a critical driver of global nutraceutical market growth, accounting for approximately 31% of the market's value in 2019. The region's market was valued at $89.6 billion in 2021 and is projected to grow at a CAGR of 8.52% through 2026 (Figure 5), reaching unprecedented levels [11]. China leads the regional market and has become the world's second-largest consumer of nutraceuticals. In 2017, the country contributed $80.9 billion, representing nearly 40% of the Asia-Pacific nutraceutical market. Despite strict regulatory frameworks, China's exports of raw materials for nutraceuticals account for approximately 65% of the global supply, highlighting its dominance in the supply chain. Similarly, Japan maintains a significant market share with its "Foods for Specified Health Use" (FOSHU) regulatory category, which has facilitated the growth of functional food and nutraceutical products. Japan's market is projected to remain strong due to its aging population and established consumer trust in health-related products. India is another rapidly expanding market in the region, valued at $2.8 billion in 2015 and expected to surpass $8.5 billion by 2022. The Indian nutraceutical market benefits from the integration of Ayurveda with modern science, with products such as ashwagandha, turmeric, and herbal teas gaining significant traction.

Europe is the third-largest nutraceutical market, with its market value reaching $79.7 billion in 2016. Although stringent regulatory frameworks constrain rapid growth, the market is expected to expand at a CAGR of 6.39% from 2018 to 2023 (Figure 5), driven by increasing health awareness and technological advancements in product development [11]. Germany leads the region, accounting for 23.02% of the market share, followed by France, Italy, and the United Kingdom. Omega-3 fatty acids and plant-based supplements are particularly popular. Additionally, the region's emphasis on high-quality research and innovation ensures that products meet rigorous safety and efficacy standards.

Latin America represents an emerging nutraceutical market with substantial growth opportunities. Brazil and Argentina dominate the region, contributing significantly to its market value. In 2005, the Brazilian nutraceutical market reached $13 billion, and it is projected to grow to $19.4 billion by 2026, at a CAGR of 7.96% (Figure 5). The

region's rich biodiversity, particularly in the Amazon rainforest, offers unique opportunities for developing plant-based nutraceuticals, provided they are sustainably managed. Additionally, increasing health awareness among middle-class and aging populations in Latin America has generated a driving demand for dietary supplements and functional foods. Consumers are particularly interested in products that address cardiovascular health, digestion, and overall immune system health.

The market for nutraceuticals is gradually emerging in the Middle East and Africa. For this reason, current market data is limited. That said, rising disposable incomes, urbanization, and increasing health awareness have begun to fuel demand in these regions. Countries such as the United Arab Emirates and South Africa are currently witnessing steady growth in the consumption of dietary supplements and functional foods. This growth is supported by the region's focus on combating lifestyle-related diseases such as diabetes and obesity.



CłËdzŃŜ p◊ Bar graph depiction of the compound annual growth rate across key global regions, focusing on North America, Asia-Pacific, Europe, Latin America, and the Middle East.

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tŃŜØŜyűłØŜ aŜŘłŐły$Y Nutraceuticals function as prophylactic agents by targeting and addressing key physiological processes contributing to disease onset. In addition to prolonging life expectancy, there is now a growing focus on maintaining a high quality of life. This change has made it clear that preventive measures are essential, rather than merely treating illnesses as they arise. This is where nutraceuticals' ability to prevent and mitigate chronic diseases by focusing on underlying biological processes comes into play [51]._A prime example of this preventive strategy is the consumption of omega-3 fatty acids, which are essential for the prevention and treatment of CVD and can be obtained from marine sources, like fish oil. It has been demonstrated that omega-3 fatty acids, particularly EPA and docosahexaenoic acid (DHA), significantly reduce the risk of cardiovascular events and mortality. According to a randomized study, the use of fish oil supplements reduced mortality caused by cardiovascular events by

29%, unexpected fatalities by 45%, and cardiovascular disorders by 30% [51]. Omega-3s also regulate the electrical conduction of the heart, lowering the risk of arrhythmias and helping prevent further complications that arise from atherosclerosis.

Nutraceuticals also show promising anticancer properties. Phenolic compounds, such as anthocyanins and flavonoids, have been shown to have potent antioxidant effects that help stop the growth of tumors in colorectal cancer [51]. Similarly, phytochemicals such as chrysin and apigenin have been shown to reduce colorectal cancer growth and metastasis by inhibiting the p38-MAPK/AKT signaling pathway.

Beyond cancer and cardiovascular diseases, nutraceuticals can serve as a great preventive measure for metabolic disorders, such as metabolic syndrome, type 2 diabetes, and obesity. These conditions are frequently brought on by oxidative stress, inflammation, and abnormalities in metabolism, structure, and function. By focusing on these underlying causes, nutraceuticals help regulate metabolic pathways. For instance, Omega-3s lower chronic inflammation by reducing the expression of cytokines such as TNF-α and IL-6. This is achieved by stimulating PPAR-γ and inhibiting key pro-inflammatory pathways, including NF-κB. This not only improves lipid metabolism but also controls hypertriglyceridemia. Furthermore, Omega-3s enhance gene expression and epigenetic markers, which impact the inflammatory response at the cellular level, and are beneficial in preventing other potential diseases that may occur [13].

Additionally, nutraceuticals help strengthen the immune system by supporting a healthy gut microbiome, which is essential for regulating immune function and reducing inflammation. The immune system is supported by promoting the growth of beneficial bacteria, such as probiotics like Lactobacillus and Bifidobacterium [1]. Nutraceuticals containing probiotics are especially beneficial in preventing inflammatory bowel disease, where inflammation is the underlying cause. Furthermore, it has been noted that sirtuin activation nutraceuticals increase Actinobacteria, which are known to promote gut and metabolic health [31]. They also enhance immune health by restoring down-regulating miRNAs, thus boosting antiviral innate immune responses. For example, studies have shown that polyphenols upregulate miRNAs, such as miR-30e, miR-101, and miR-150, and inhibit viral replication through multiple pathways involving mTOR. This blocks viral replication cycles and enhances interferon-mediated responses. Zinc has also been shown to act as a cofactor in many immune enzymes, affecting miRNA synthesis and stability, resulting in reduced oxidative stress and improved function of NK cells, which are crucial in early viral defense [21].

Nutraceuticals provide a sustainable and natural approach to disease prevention by treating the underlying mechanisms of oxidative stress, inflammation, and metabolic dysfunction.

Brain Function: Alzheimer's Disease: Alzheimer's disease (AD) is a progressive brain disorder that impairs memory and thinking abilities. It is responsible for 60–80% of global dementia cases. Molecular drivers of AD include (Aβ) plaques, which disrupt neuronal communication and cause inflammation, tau tangles that impair microtubule function, and glutamate toxicity leading to neuronal damage. These changes result in significant shrinkage of brain regions, such as the cortex and hippocampus. Genetic factors, such as the APOE4 allele, exacerbate these processes by impairing amyloid clearance and promoting inflammation [10,59]. Oxidative stress, resulting from an excess of reactive oxygen species (ROS), also plays a crucial role in AD development. It exacerbates Aβ plaque formation and tau tangle

aggregation, creating a cycle of neurodegeneration. Moreover, oxidative stress increases with age, further accelerating mitochondrial dysfunction, neuronal damage, and cognitive decline [10]. Nutraceuticals can inhibit the development of AD via various cellular mechanisms. For example, curcumin, a compound found in turmeric, exhibits various beneficial mechanisms against AD. It binds directly to Aβ plaques, preventing their aggregation, and promotes their removal from the brain, further mitigating synaptic dysfunction. Its antioxidant properties reduce ROS levels and oxidative stress markers, while its anti-inflammatory effects inhibit cytokines such as TNF-α and IL-6 by targeting the NF-κB signaling pathway. Curcumin also modulates tau protein, reducing its hyperphosphorylation and stabilizing microtubules. Animal studies demonstrate its potential in improving memory and learning abilities in AD models [10,59].

Similarly, resveratrol, found in red grapes, activates the SIRT1 protein. SIRT1 activation reduces Alzheimer's-related pathologies by increasing α-secretase activity, which moves amyloid precursor protein processing away from Aβ production, and acetylation of tau proteins, hyperphosphorylation, and causes proteasomal degradation, limiting neurofibrillary tangles. Resveratrol also neutralizes ROS and reduces neuroinflammation by inhibiting nuclear factor kappa B (NF-κB) signaling. Further, clinical evidence suggests that resveratrol stabilizes Aβ levels and reduces neuroinflammatory markers, such as matrix metalloproteinase-9, which regulates blood-brain barrier permeability [10].

.ǊI-ʎyʃ CdzyŎǘʎƨyY tI-ǊʅʎyăƨyΩă 5ʎăŜI-ăŜ: Parkinson's disease (PD) is a degenerative disorder characterized by the loss of dopamine-producing neurons in the substantia nigra pars compacta and the accumulation of Lewy bodies, which contain misfolded α-synuclein proteins. This leads to both motor and nonmotor symptoms, including bradykinesia, resting tremors, and cognitive decline [28]. The etiology of PD includes oxidative stress, mitochondrial dysfunction, neuroinflammation, protein aggregation, and gut dysbiosis. However, these underlying mechanisms are not adequately addressed through conventional treatments, which focus on dopamine replacement. This leads to limited long-term treatment success and unwanted side effects [19]. Nutraceuticals, on the other hand, have demonstrated promise in slowing down the progression of PD by manipulating these cellular mechanisms. Some examples are epigallocatechin gallate (EGCG), CoQ10, and ginsenoside.

One example is EGCG, a major catechin in green tea. Studies conducted on MPTP-induced Parkinsonism in animal models indicate EGCG's role in regulating oxidative stress and protecting against dopaminergic degeneration [62]. For example, EGCG can cross the blood-brain barrier, allowing it to reinforce the brain's vulnerable dopaminergic neurons directly. EGCG can also scavenge the free radicals that would otherwise lead to oxidative stress and contribute to PD development. More specifically, EGCG acts as an iron chelator due to its catechol group, which can attach to redox-active ferrous iron, preventing its buildup in the substantia nigra and worsening oxidative damage. Additionally, EGCG has been demonstrated to modulate protein kinase C activity and enhance natural antioxidant defense systems, both of which are protective benefits that contribute to slowing the progression of PD.

CoQ10 is a key mitochondrial electron transport chain component. It is a potential therapeutic agent for

PD due to its ability to restore mitochondrial function. PD-related mitochondrial dysfunction is linked to impaired complex I activity in the ETC, which then causes a reduction in ATP synthesis and an increase in ROS production. CoQ10 acts as an electron transporter between complex I and III, thereby contributing to an efficient electron transport system and protecting dopaminergic neurons from oxidative stress [19]. Moreover, CoQ10 is a powerful antioxidant that combats hydrogen peroxide and superoxide radicals generated by mitochondrial dysfunction.

Ginsenoside, a phytoestrogen derived from ginseng, exhibits neuroprotective effects by maintaining glutathione levels and modulating various inflammatory pathways, including the ROS-NFκB, JNK, PI3K/AKT, ERK, and IGF-1 receptor signaling pathways [19]. Ginsenoside also regulates iron transport proteins, reducing iron-induced toxicity and oxidative damage characteristic of PD due to iron accumulation in the substantia nigra [19].

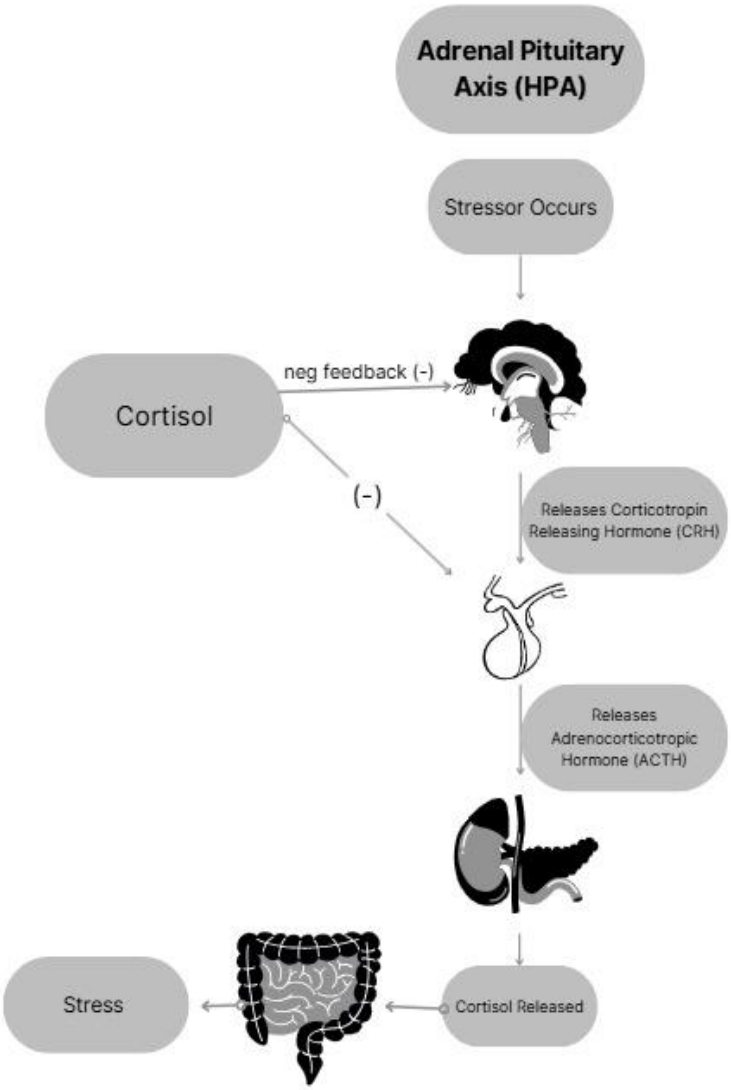

Figure 6. Adrenal Pituitary Axis. This Figure illustrates the Hypothalamic-Pituitary-Adrenal (HPA) axis, the body's central stress response system. It shows how the brain communicates with the adrenal glands to release stress hormones like cortisol as a response to a stressor, therefore inducing the feeling of stress.

Stress Management: Nutraceuticals play a crucial role in managing and preventing stress by regulating the body's physiological response to stimuli and supporting adrenal function. Long-term stress triggers the hypothalamic-pituitary-adrenal (HPA) axis, which ultimately results in the release of cortisol (Figure 6). This can be detrimental if it is prolonged and in excess [3]. Adaptogens, minerals, and vitamins (Table 2) are examples of nutraceuticals that help balance cortisol levels and enhance the body's ability to withstand stress by regulating the HPA axis.

Adaptogens are natural substances that control the release of stress hormones. Ashwagandha, also known as *Withania somnifera*, is one of the most extensively studied adaptogens for stress reduction. It has been shown to reduce stress by controlling the release of the corticotropin-releasing factor from the hypothalamus, thereby preventing the overactivation of the HPA axis and lowering overall cortisol production [3]. Additionally, Ashwagandha enhances the brain's gamma-aminobutyric acid (GABA) receptors, which reduces neuronal excitability, resulting in a calming and anxiolytic effect (Table 2).

Magnesium has also been found to play a vital role in stress reduction by regulating N-Methyl-D-Aspartate (NMDA) receptor activity in the brain. The NMDA receptor promotes excitatory neurotransmission, but overactivation can lead to neuronal hyperexcitability and increased vulnerability to stress. Magnesium functions as a natural NMDA receptor antagonist, reducing excitotoxicity and promoting relaxation [3]. Magnesium also inhibits excessive CRF release, which controls HPA axis activity, lowering cortisol secretion and lessening the physiological effects of long-term stress (Table 2). Further, magnesium deficiency has been linked to increased sympathetic nervous system activity, which intensifies stress responses.

Zinc plays a crucial role in the regulation of anxiety by modulating neurotransmitter activity, supporting antioxidant defenses, and maintaining immune system function and balance. Like magnesium, zinc also inhibits NMDA-type glutamate receptors, which can help prevent excitotoxicity, heightened neuronal activity, and anxiety. However, zinc also acts as a cofactor in enzymes that are involved in the synthesis and regulation of key neurotransmitters, including serotonin, GABA, and glutamate. Simultaneously, zinc enhances GABAergic signaling, which promotes neuronal inhibition and emotional calmness. Beyond neurotransmission, zinc is vital for the brain's antioxidant defense, reducing ROS, and further limiting oxidative stress. Zinc also regulates immune signaling in the brain by attenuating the production of pro-inflammatory cytokines that are elevated in anxiety and other mood disorders. More, in both animal and human studies, zinc deficiency is consistently linked with heightened anxiety. So, there is therapeutic value in the prevention or treatment of anxiety-related conditions by ensuring adequate zinc levels [57].

Table 2. Mechanisms of Nutraceuticals that Help Mitigate Stress.

Nutraceutical	Sources	Mechanism of Action
Omega-3 Fatty Acids	Fatty fish, flaxseeds, walnuts	Omega-3s, especially DHA, support serotonin and dopamine production, essential for mood regulation. Helps mitigate inflammation linked to mental health disorders like anxiety and depression. EPA and DHA play a key role in maintaining brain structure, supporting cognitive function, and reducing the risk of age-related cognitive decline. Alleviate symptoms of depression and anxiety, especially in individuals with low baseline levels. Help the body manage stress by balancing the production of stress hormones. [43]
B- Vitamins	Whole grains, meat, eggs, leafy greens	B-vitamins, particularly B6, B9 (folate), and B12, support the synthesis of key neurotransmitters like serotonin, dopamine, and GABA, crucial for mood regulation. B1 (thiamine), B2 (riboflavin), and B3 (niacin) are critical for energy production, supporting overall brain function and preventing mental fatigue. Folate (B9) and B12 are essential for maintaining a balanced mood, and deficiencies have been linked to higher rates of mood disorders like depression and anxiety. B12 and B9 help prevent cognitive decline, promoting sharper memory and mental clarity. B1 and B6 play a role in regulating the nervous system, helping to reduce anxiety symptoms. Have been shown to improve emotional regulation and mood, particularly in those with deficiencies. [43]
Probiotics	Yoghurt, kefir	Probiotics enhance serotonin, dopamine, and GABA production, essential for regulating mood, anxiety, and stress levels. Reduce systemic inflammation that contributes to mental health disorders such as anxiety and depression. Have demonstrated efficacy in reducing symptoms of anxiety and depression through the gut-brain axis. Help stabilize mood and may reduce symptoms in conditions such as bipolar disorder. Support brain function and may slow cognitive decline over time. Improve the body's ability to cope with stress, enhancing emotional regulation and reducing the effects of PTSD and anxiety. [43]
Curcumin	Turmeric	Antioxidant properties reduce oxidative stress in the brain, protecting cells from damage caused by chronic stress. Reduces brain inflammation by inhibiting pro-inflammatory cytokines and enzymes, improving mood and cognitive function. Supports brain health by promoting neurogenesis and protecting against neurodegenerative damage. Has been shown to alleviate symptoms of anxiety and depression through its anti-inflammatory and antioxidant actions. By improving neuroplasticity and protecting against neural damage, Curcumin helps maintain mental clarity under chronic stress.

Nutraceutical	Sources	Mechanism of Action
		Enhances the brain's ability to handle stress-induced damage, reducing the long-term effects of cortisol elevation. [43]
Ashwagandha	*Withania somnifera* (Indian ginseng)	Modulates the release of corticotropin-releasing factor (CRF) and adrenocorticotropic hormone (ACTH), lowering cortisol levels and preventing overactivation of the HPA axis during stress. Improves GABA receptor function, reducing neuronal excitability, inducing calming effects, and reducing anxiety. Supplementation lowers serum cortisol levels, mitigating the physiological effects of chronic stress. Improves cognitive function under stress, protecting brain cells from damage caused by cortisol and promoting overall brain health. Enhances the body's natural ability to handle stress, reducing anxiety and depressive symptoms. Helps increase the body's emotional resilience by regulating hormones and supporting neurochemical balance.[3]
Magnesium	Leafy greens, nuts, seeds, whole grains	Magnesium reduces excitotoxicity by modulating NMDA receptor activity, promoting relaxation and calming overactive brain regions. Magnesium inhibits excessive CRF release, which helps lower cortisol production and dampens the body's stress response. Reduces neuronal excitability by acting on the NMDA receptors, which helps in alleviating anxiety. Controls sympathetic nervous system activity, preventing overactivation during stressful situations. Balances neurotransmitter function and reduces anxiety symptoms by inhibiting excess cortisol and supporting GABAergic activity.[3]
Gingerol	Ginger	Modulates GABA receptors by binding to allosteric sites on α-γ subunits, enhancing GABAergic inhibition and promoting a calm feeling. Interacts with key residues (e.g., Phe77, Tyr210) to stabilize GABA receptor activity, like the common allopathic medicine, diazepam. Crosses the blood–brain barrier and binds plasma proteins, enabling effective CNS action, exerting neuroactive effects Has antioxidant effects via vitamin C and anthocyanins, protecting neurons from oxidative stress, a key factor in the pathogenesis of anxiety. Inhibits CYP2D6 and CYP3A4, suggesting potential synergy or interaction with existing anxiolytics. [28]

Table 2. This table explains how nutraceutical compounds, such as Omega-3 fatty acids, B vitamins, probiotics, Curcumin, ashwagandha, and magnesium, affect mood, cognition, and the stress response at the biochemical and physiological levels.

Cardiovascular Diseases: CVDs, including hypertension, atherosclerosis, myocardial infarction, and diabetes, are a rising problem across the globe. They have prompted a growing interest in preventative measures, like nutraceuticals, that go beyond conventional pharmacological interventions.

Flavonoids are a group of polyphenolic compounds found in many plant-based foods, which have been linked to a decreased risk of coronary heart disease, stroke, and

other CVDs. These compounds enhance nitric oxide metabolism, along with endothelial function, both of which are essential for maintaining vascular health. For example, research indicates that flavonoids derived from cocoa increase the bioavailability of NO, protect the vascular endothelium, and reduce factors that contribute to CVDs, such as insulin resistance and systemic inflammation [8]. Oligomeric procyanidins are a specific type of cocoa-derived flavonoid that have been demonstrated to improve peripheral vasodilation, enhance antioxidant capacity, and lower blood pressure in numerous clinical trials [8].

Spirulina (*Arthrospira platensis*) is a blue-green microalga that. It contains peptides that have demonstrated angiotensin-converting enzyme inhibitory activity, which leads to a reduction in blood pressure, like pharmaceutical agents like captopril. Animal studies have shown that spirulina regulates the renin-angiotensin system by downregulating harmful components, such as ACE and angiotensin II type 1 receptors, while upregulating protective elements, including ACE2 and the Mas receptor. Additionally, human clinical trials have shown that a decamer peptide derived from spirulina has been demonstrated to promote vasorelaxation and lower diastolic blood pressure by activating the PI3K/Akt/eNOS signaling pathway. In hypertensive patients, taking spirulina for several weeks significantly reduced both systolic and diastolic blood pressure, improved vascular stiffness, and enhanced antioxidant enzyme levels. Spirulina has also been shown to improve heart health by lowering levels of vascular adhesion molecules and endothelin-1, which cause blood vessels to constrict and adhere to white blood cells, leading to inflammation [8].

Moderate red wine consumption has been linked to CVD prevention due to its richness in polyphenols like flavonoids, resveratrol, and proanthocyanidins. These compounds have antioxidant and anti-inflammatory properties that help reduce vascular inflammation, oxidative stress, and platelet aggregation while enhancing nitric oxide (NO) production and endothelial function. In addition to polyphenols, wine contains melatonin, which supports cardiovascular health by improving the circadian rhythm, lowering blood pressure, and enhancing vascular function through its antioxidant effects. Furthermore, phytosterols such as β-sitosterol, stigmasterol, and campesterol decrease cholesterol absorption in the gut, lowering plasma total and LDL cholesterol levels. While the ethanol in wine may counteract some of these protective effects when consumed excessively, moderate intake allows the synergistic action of these phytochemicals to contribute significantly to cardiovascular health [22].

Omega-3 polyunsaturated fatty acids, especially eicosapentaenoic acid (EPA) and DHA, are essential dietary components with significant anti-inflammatory and cardioprotective properties. The human body cannot produce these fatty acids in sufficient amounts, so regular intake is necessary. Their anti-inflammatory action involves arachidonic acid displacement from cell membranes, which reduces the production of pro-inflammatory eicosanoids through the COX pathway. EPA and DHA also suppress cytokine production and the expression of adhesion molecules, which support the formation of specialized lipid mediators, including resolvins, proteins, and maresins. These mediators actively resolve inflammation through COX and LOX enzymes [47]. Clinical evidence has also shown that EPA and DHA supplementation significantly reduces pro-inflammatory cytokines, such as IL-6, IL-1β, TNF-α, and hsCRP. DHA often produces more pronounced improvements in lipid profiles, including greater reductions in triglycerides and increases in HDL-C [47].

Clinical evidence also shows that a combination of nutraceuticals, such as monacolin K (from red yeast rice), berberine, and bergamot, significantly lowered harmful

LDL cholesterol levels by about 25 mg/dL in 30 days without causing any serious adverse effects. Monacolin K functions similarly to statin drugs by reducing cholesterol production. Meanwhile, berberine helps the liver remove more LDL from the blood, and bergamot aids in both lowering cholesterol and reducing inflammation. Unlike many conventional drug treatments, which can cause side effects like muscle pain or liver issues, this nutraceutical blend was well-tolerated, demonstrating that natural supplements, when carefully formulated and monitored, can provide a safe and effective option for lowering cholesterol and reducing the risk of heart disease [15].

Bone Health: Bone health is maintained through a balance between bone formation, conducted by osteoblasts, and bone resorption, performed by osteoclasts. The key to osteoblast activity is the transcription factor RUNX2, which is regulated by estrogen and parathyroid hormone (PTH). These hormones help increase RUNX2 levels by blocking the activity of an enzyme called GSK-3β, allowing another protein, β-catenin, to remain stable and active. Estrogen does this through NO and cGMP signaling, while PTH works through cAMP and PKA signaling pathways. Enzymes such as AMPK and SIRT1 protect RUNX2 through phosphorylation and deacetylation, while also promoting autophagy and the survival of osteoblasts and osteocytes, thereby maintaining a balance between the two. On the other hand, the formation and activity of osteoclasts are regulated by NFATc1, which is stimulated by RANKL binding to RANK and the activation of NF-κB, AP-1, and ROS-mediated signaling cascades. When PLC-γ is activated, it causes an increase in calcium levels inside the cell, leading to the activation of a protein called calcineurin. This protein then activates NFATc1 by removing a phosphate group. This allows it to enter the nucleus and increase its production.

Nutraceuticals support bone health not only by stimulating anabolic pathways, but also by inhibiting catabolic processes. For instance, compounds like berberine activate AMPK, while melatonin, ferulic acid, and nicotine mid-ribosome activate SIRT1, supporting osteoblast survival and RUNX2 expression while suppressing apoptosis. The same compounds decrease NFATc1 activity. Additionally, nutraceuticals like sulforaphane and lipoic acid activate Nrf2, helping to neutralize oxidative stress, which preserves osteoblast viability and reduces the bone-resorbing activity of osteoclasts. Not only that, but high doses of biotin, taurine, and N-acetyl cysteine (NAC), derived from the amino acid cysteine, increase signaling molecules like cGMP and H2S, which factor in osteoblast function and bone matrix production, thereby decreasing oxidative and inflammatory damage [35]. That said, nutraceuticals can also counteract inhibitory signaling pathways. For instance, flavonoids such as quercetin and kaempferol inhibit CK2, a kinase that negatively regulates the BMP pathway, which is essential for bone formation. Additionally, in inflammation-driven bone loss, nutraceuticals that enhance SIRT1 or reduce ROS, such as spirulina and berberine, not only lower proinflammatory cytokine production through NF-κB/AP-1 inhibition but also mitigate the bone-depleting side effects of glucocorticoids by suppressing PPARγ and SFRP5 expression. By promoting osteogenesis and inhibiting catabolic activity, these nutraceuticals exert effects on multiple pathways to preserve skeletal integrity [35].

Cancer Prevention & Treatment: Nutraceuticals are currently emerging as potent therapeutic agents in cancer treatment due to their bioactive elements' ability to modulate key cancer pathways. This makes them promising candidates not only for cancer prevention and treatment, but for mitigating the side effects of treatments such as chemotherapy and radiation [1].

Cancer stem cells (CSCs) play a crucial role in tumor growth and metastasis due to their ability to self-renew. CSC survival and proliferation depend on several signaling pathways [12]. Nutraceuticals can block these pathways, lowering CSC survival and tumor formation. Curcumin blocks the Wnt/β-catenin, Notch, and Hedgehog pathways, and resveratrol inhibits the NF-κB and STAT3 signaling pathways (Figure 7). By reducing the number of CSCs, these nutraceuticals increase the vulnerability of tumors to chemotherapy and radiation. EGCG is another nutraceutical that prevents tumor formation but does so by inducing apoptosis in CSCs. Through the stimulation of the p53 pathway and disruption of mitochondrial activity [12].

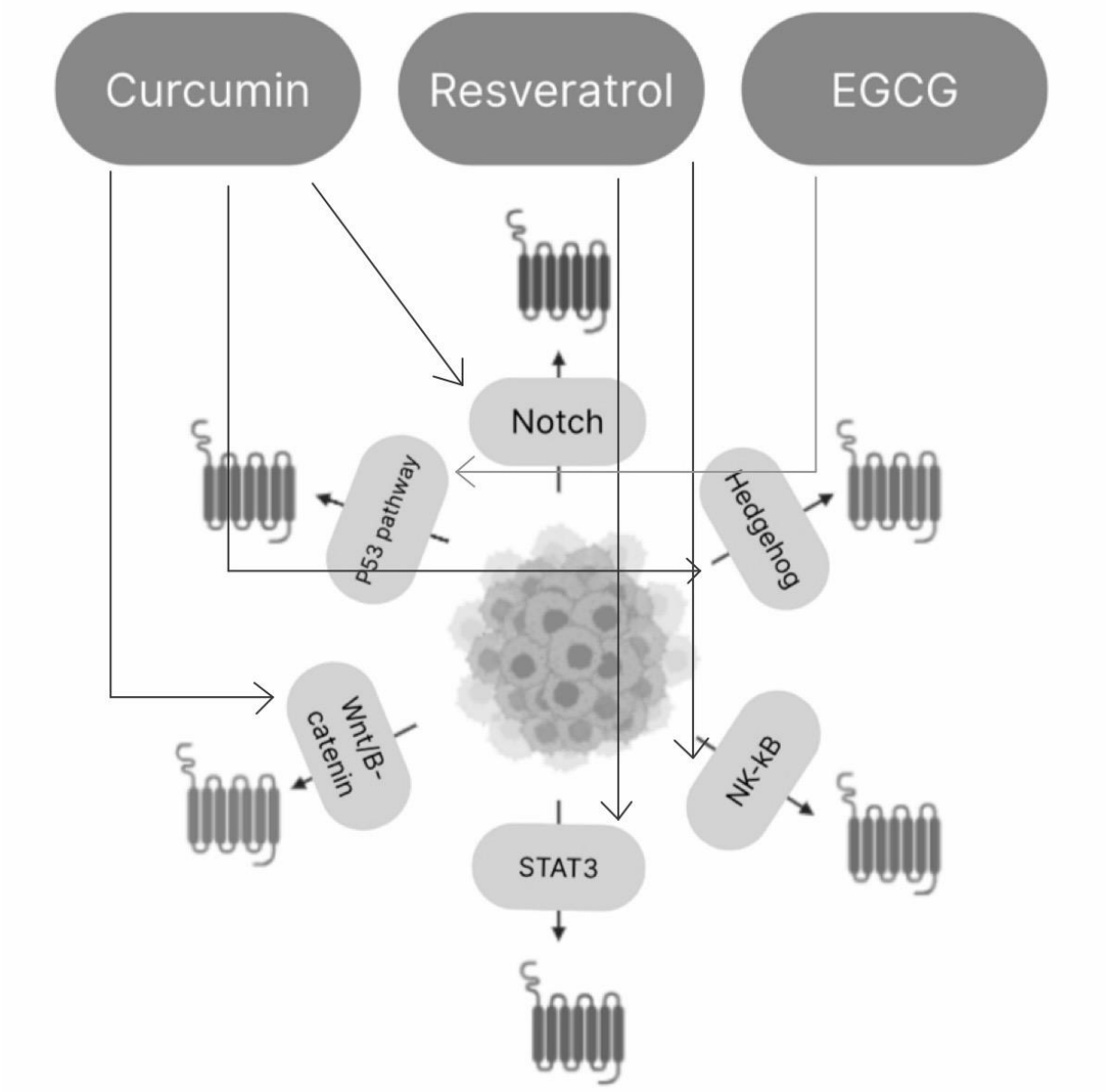

Figure 7. Nutraceutical Inhibition of Cancer Stem Cell Signaling Pathways. This figure shows how nutraceuticals like curcumin, resveratrol, and EGCG inhibit key signaling pathways such as Wnt/β-catenin, Notch, STAT3, NF-κB, Hedgehog, and p53, which support CSC survival and tumor growth. By blocking these pathways, these compounds reduce CSC self-renewal, enhance chemotherapy sensitivity, and promote apoptosis. This highlights the potential of nutraceuticals to prevent tumor recurrence and improve treatment outcomes.

Another example is bergamot extract (BEO), rich in flavonoids. BEO has been observed to induce cancer cells to undergo apoptosis by causing cell cycle arrest during the G0–G1 phase and promoting pro-oxidant activity that damages the cancer cells' DNA. According to in vitro studies, BEO exhibits antitumor effects on many kinds of cancer, including breast and prostate [35].

Similarly, oleuropein, a polyphenol primarily found in olives and olive leaves, has demonstrated anticancer effects against various cancer types, including lung, colon, prostate, and breast cancer. The primary mechanism by which oleuropein inhibits cancer is the modulation of apoptotic pathways. By upregulating cyclin-dependent kinase inhibitors and altering the expression of tumor suppressor genes, including p53 and p21, it causes cell cycle arrest. Oleuropein also influences the c-Met proto-oncogene and MAPKs, two molecules implicated in the development and progression of cancer [37]. Oleuropein has the potential to be used as an adjuvant in cancer therapy, as recent research has demonstrated that it can protect cells from the harmful effects of cisplatin and increase the efficacy of other traditional cancer treatments.

Quercetin, a flavonoid found in various fruits, vegetables, and plants, has also been recognized for its anticancer properties. Quercetin promotes apoptosis by modulating several key apoptotic pathways. It has been shown to cause cell cycle arrest by downregulating cyclins and cyclin-dependent kinases in various cancer types, including ovarian, leukemia, and osteosarcoma. Additionally, quercetin causes mitochondrial dysfunction and releases cytochrome C, which triggers the apoptotic cascade by activating pro-apoptotic proteins such as Bak and Bax, and downregulating anti-apoptotic proteins like Bcl-2 [35]. Quercetin's ability to inhibit cell proliferation, metastasis, and angiogenesis has been well-documented, particularly in models of breast, prostate, and lung cancer. It has also been observed to have enhanced effects when combined with other drugs like vincristine, making it a promising option for cancer treatment.

Another flavonoid-rich compound, black rice, has been suggested to have anticancer properties against several types of cancer cells. Studies using lab-grown cancer cells from the breast, colon, cervix, liver, and other tissues have found that black rice extracts, especially those containing cyanidin 3-glucoside and peonidin 3-glucoside, can slow the growth of cancer cells, trigger apoptosis, and prevent them from invading nearby tissues. These effects are thought to occur through the downregulation of the MMP-2 and MMP-9 enzymes, which usually help cancer cells spread. Furthermore, combining cyanidin 3-glucoside and peonidin 3-glucoside with chemotherapy drugs, such as doxorubicin, may enhance treatment effects. Though most research has been in lab settings, the evidence suggests that including black rice in the diet could support both cancer prevention and treatment, mainly when used alongside conventional therapies like chemotherapy and radiation [45]

The immune system is crucial for identifying and eliminating abnormal cells before they develop into serious cancers. The body's capacity to identify and eliminate potential cancer cells can be enhanced by bioactive substances like beta-glucans, which are found in oats and mushrooms, and can increase the activity of natural killer (NK) cells and macrophages [1]. Vitamin D, another crucial nutraceutical, strengthens the body's defenses against the early stages of cancer by activating the Vitamin D receptor (VDR), which causes apoptosis, stops the progression of the cell cycle, and inhibits angiogenesis [1]. By targeting these early biomarkers and immune mechanisms, nutraceuticals can significantly lower the overall risk of cancer, especially for at-risk populations.

Nutraceuticals help mitigate the adverse effects of traditional cancer treatments and are also used in cancer

prevention. For instance, curcumin and EGCG, found in turmeric and green tea, respectively, can reduce the gastrointestinal toxicity and exhaustion that are common adverse effects of chemotherapy. These substances not only alleviate the burden of treatment but also enhance the overall efficacy of chemotherapy by increasing patient resilience [5].

Additionally, compared to conventional cancer treatments, nutraceuticals are often more affordable, opening cancer care to a broader range of people. Nutraceuticals are revolutionizing modern medicine by providing individualized therapy options based on each patient's unique genetic and biochemical profile. By combining the benefits of both conventional and natural medicines, this approach is helping to create a more comprehensive and effective cancer management plan that enhances patient outcomes and quality of life [1].

Boosting Immune Competence: Nutraceuticals are increasingly recognized for modulating immune responses through many different biochemical pathways. Their immunomodulatory activity varies from regulating cytokine expression to influencing leukocyte function and maintaining immune homeostasis. For example, vitamin C, probiotics, zinc, and vitamin D have demonstrated significant effects on innate and adaptive immunity through specific signaling cascades and cellular mechanisms [7].

Vitamin C has significant immunomodulatory effects through its antioxidant properties and direct interaction with immune signaling pathways. One of its main actions is the inhibition of NF-κB, a key transcription factor that controls the production of proinflammatory cytokines like TNF-α, IL-1β, and IL-6. By preventing NF-κB activation, vitamin C reduces the rise of cytokines typically linked to acute respiratory infections and inflammatory lung damage. Furthermore, vitamin C interferes with the GM-CSF signaling pathway, decreasing oxidative damage in host defense cells by modulating redox-sensitive mechanisms. At the cellular level, vitamin C enhances the function and growth of T, B, and natural killer cells. It accumulates in leukocytes, especially neutrophils and monocytes, where it stabilizes microtubules essential for chemotaxis and cell migration. Vitamin C also affects antibody production by supporting lymphocyte differentiation and survival, leading to stronger humoral responses.

Probiotics, especially strains like *Lactobacillus rhamnosus GG* and *Bifidobacterium lactis HN019*, modulate immunity by interacting with gut-associated lymphoid tissue (GALT) and influencing both innate and adaptive immune responses. They act through pattern recognition receptors such as Toll-like receptors (TLRs) on epithelial cells and dendritic cells, which initiate downstream signaling via the NF-κB and MAPK pathways, leading to regulated cytokine production. Probiotic exposure can enhance the expression of co-stimulatory molecules such as CD80/CD86 on antigen-presenting cells, facilitating effective T cell activation. Furthermore, probiotics influence the balance of T helper cell subtypes (Th1, Th2, Th17) and induce regulatory T cells through TGF-β and IL-10 signaling, supporting immune tolerance and preventing overactivation. Notably, some strains stimulate proinflammatory cytokines like IL-18 and IFN-α during viral infections to boost innate immunity, while others promote anti-inflammatory responses to maintain homeostasis. This dual action stimulates a strong response while preventing excessive inflammation, making probiotics powerful agents in immune regulation, especially for respiratory and gastrointestinal infections [7].

Zinc is involved in innate and adaptive immune responses. It is essential for over 300 enzymatic reactions, acting as both a structural element and a second messenger in intracellular signaling. It supports the cytotoxic activity of NK cells and neutrophils, as well as the function of macrophages through stabilization of

membranes and the cytoskeleton. Zinc's immunomodulatory effects include downregulation of NF-κB activity, which suppresses the release of proinflammatory cytokines such as IL-1, IL-6, and TNF-α. Furthermore, zinc influences the FOXP3-TGF-β axis, which is responsible for the differentiation and function of Tregs in adaptive immunity. This pathway helps maintain immune homeostasis and prevents autoimmunity by promoting tolerance. Zinc also modulates cytokine signaling, enhancing IL-2 and IL-6 production while downregulating IL-4, shaping T helper cell responses. Zinc deficiency impairs both CD4+ and CD8+ T cell responses and reduces lymphocyte proliferation, leading to compromised immunity and heightened susceptibility to infection [7].

Vitamin D plays an important role in modulating both the innate and adaptive immune responses as well. One of its key functions is enhancing the expression of antimicrobial peptides like cathelicidin and β-defensins, which directly neutralize pathogens and help recruit immune cells to infection sites. Vitamin D upregulates pattern recognition receptors such as TLR2 and TLR4 on monocytes within the innate immune system, improving pathogen detection. Additionally, vitamin D signaling via the vitamin D receptor can activate the PI3KC3 pathway, boosting ROS and iNOS production in macrophages, aiding in the clearance of infected cells. Vitamin D also influences antigen presentation by reducing the expression of co-stimulatory molecules such as CD80, CD86, CD40, and MHC-II on dendritic cells and macrophages, skewing their phenotype toward a tolerogenic state. These tolerogenic dendritic cells, in turn, promote the differentiation of regulatory T cells and suppress proinflammatory Th17 responses by reducing IL-12 and IL-23 secretion. In adaptive immunity, vitamin D indirectly supports T helper 2 cell differentiation through upregulation of transcription factors such as c-Maf and GATA3, encouraging the release of anti-inflammatory cytokines like IL-4, IL-5, and IL-10. Moreover, in some viral infections, vitamin D has been observed to reduce pro-inflammatory chemokines such as CXCL10 and CCL19 in infiltrating macrophages, thereby limiting any excessive immune cell recruitment and tissue damage. Collectively, these mechanisms highlight how vitamin D enhances host antiviral defense while simultaneously preventing overactivation of the immune response, thus promoting a balanced and effective immune state in respiratory infections [45].

Caution and Considerations in Nutraceutical Use FDA/ WHO Concerns: Nutraceuticals have the potential to prevent or treat various health conditions. However, several factors need to be considered concerning their safety and regulation. The regulation of nutraceuticals remains a complex issue that is still unresolved, particularly for the Food and Drug Administration (FDA) and the World Health Organization (WHO). This complexity arises from multiple reasons, primarily the lack of an internationally accepted definition of nutraceuticals, which makes it difficult to apply consistent regulatory standards. As a result, each country has its own method of monitoring "foodstuffs." For example, in the United States, the Dietary Supplement Health and Education Act (DSHEA) of 1994 permits manufacturers to sell nutraceuticals without prior FDA approval, provided they do not make explicit claims about treating diseases with their products.

In contrast, the EFSA follows a more rigorous approach in which companies are required to get approval for any health claims made on nutraceutical packaging. This approval process includes a thorough analysis of scientific evidence supporting the claim. However, despite being more stringent than the US, Europe still does not officially define the term "nutraceutical," leaving these products under the same category as food supplements, functional foods, or

medicinal foods, depending on the product's composition [52].

In other regions, such as Canada and Japan, nutraceuticals are regulated more strictly than in the U.S. but more leniently than in Europe. In Canada, nutraceuticals are treated as Natural Health Products (NHPs), requiring manufacturers to obtain a product license that demonstrates safety, quality, and efficacy. Meanwhile, Japan classifies many nutraceuticals under its FOSHU category, requiring government approval before products can be marketed with specific health claims [49]. The Codex Alimentarius, developed by the WHO and the UNFAO, has become an international guideline to provide a basic standard for food safety, including nutraceuticals. However, it still didn't offer a clear regulatory framework, so it still gave countries the freedom to have their own policies, which again makes it difficult to have consistent global regulation of nutraceuticals.

Controversy: Many nutraceuticals have been banned in many different countries due to concerns about safety and efficacy. For example, bitter orange extract is prohibited in the USA and India. The extract initially gained popularity due to the belief that it would cause weight loss and serve as a performance-enhancing supplement. However, it contains p-synephrine, a stimulant that elevates blood pressure, increases heart rate, and potentially causes cardiovascular complications. Further, it is structurally like ephedrine, another banned stimulant. For the fear that it may pose health risks in athletes who are vulnerable to heart-related issues, organizations like the National Collegiate Athletic Association have forbidden their use [33].

Another example is kava or *Piper methysticum*, which has been banned or restricted in many countries due to its potential for hepatotoxicity. Kava has been used in the South Pacific for ceremonial, social, and medicinal purposes, serving as a remedy for anxiety and insomnia. However, the risk of liver toxicity has led to regulatory actions. In 2002, the FDA issued an advisory warning against kava-derived products, prompting European countries, including France, Germany, and Switzerland, to withdraw kava from their markets outright. Countries like Australia and New Zealand permit the sale of kava, but regulate it tightly, allowing for a daily intake of kavalactones —the active compound in kava — to be limited to 250 mg per day [57].

There is also a ban on comfrey in the United States because it contains pyrrolizidine alkaloids, which were initially used to treat various internal and external ailments, including chronic bronchial conditions, gastritis, duodenal ulcers, colitis, rheumatism, arthritis, osteoporosis, multiple sclerosis, amyotrophic lateral sclerosis, and open wounds. However, it was later found to be toxic to the liver and linked to veno-occlusive disease (VOD). Pyrrolizidine alkaloids have also been shown to be carcinogenic and damaging to other tissues in the body. Due to these serious health concerns and the lack of evidence for a safe dosage, the FDA has called for the removal of comfrey-containing dietary supplements from the market [16].

Lack of Scientific Evidence: While nutraceuticals are promoted for their preventive benefits, many of these claims lack support from randomized clinical trials, which are regarded as the gold standard in medical research. A major issue is that much of the existing research on nutraceuticals relies on in vitro (test tube) and in vivo (animal) studies, which do not always translate effectively to human physiology. Many nutraceuticals contain bioactive compounds that may show efficacy in isolated laboratory conditions but fail to demonstrate the same effectiveness when consumed in real-world dietary settings [52]. This may be due to low bioavailability and rapid metabolism, making it difficult to achieve the desired results with regular consumption. Therefore, rigorous safety assessments and well-designed clinical

studies are crucial before nutraceuticals can be confidently recommended for human use, ensuring both their effectiveness and safety in the target population.

This lack of robust human clinical data represents a critical research gap that undermines the credibility and therapeutic potential of nutraceuticals. Without clear evidence of safety, efficacy, and optimal dosage in human populations, consumers and healthcare providers are left to navigate an uncertain landscape, which can lead to misuse, unmet health expectations, or even adverse effects. Addressing this gap is essential to legitimize nutraceuticals within evidence-based medicine and fully utilize their potential in preventive healthcare.

Contamination Risks: Nutraceuticals can pose significant risks if contaminated with heavy metals, mycotoxins, pesticides, toxic botanical compounds, or microbial agents. When presented with these contaminants, the safety and quality of nutraceuticals can be compromised, leading to detrimental health effects, including organ toxicity, carcinogenicity, and adverse drug interactions.

Toxic heavy metals, including mercury, arsenic, cadmium, and lead, can accumulate in nutraceuticals during harvesting, processing, and storage, and long-term exposure can cause neurological damage, kidney dysfunction, or immune system damage. Similarly, pyrrolizidine alkaloids can contaminate various foods and nutraceuticals. They are among the most toxic alkaloids present in several plant species, as they can react with proteins to cause abnormal mitosis, tissue necrosis, and cellular dysfunction [1].

Pesticide residues are common contaminants in plant-based nutraceuticals due to widespread agricultural use. These residues may still be found in the final product and can cause toxicity, hormonal disruption, and an increased risk of cancer if the consumer is exposed over time [1].

Mycotoxin contamination occurs when fungal metabolites enter nutraceuticals and remain undetected. Exposure to mycotoxins can cause liver damage, immune suppression, and an increased likelihood of cancer [1]. A Polish study demonstrated the prevalence of microbial contamination, finding that 86.8% of 152 examined nutraceutical samples were contaminated with fungi, and 92.1% of them were contaminated with bacteria [1]. The stability and safety of nutraceuticals rely on proper manufacturing and storage conditions, lest they become breeding grounds for microbes.

In addition to microbial and chemical contamination, unintended interactions between nutraceuticals and other compounds may also have adverse effects. For example, peppermint oil could reduce the efficacy of prescription medication, as it interacts with cytochrome P450 enzymes, which are responsible for the metabolism of certain prescription drugs. Also, nutraceuticals that are high in tyramine can interact with certain antidepressants called monoamine oxidase inhibitors, causing irregular heartbeats, dangerously high body temperature, bleeding in the brain, or even a life-threatening spike in blood pressure [11].

To reduce these risks, regulatory agencies like the FDA and WHO need to enforce stricter safety standards for nutraceuticals. This includes establishing more comprehensive labeling requirements that fully disclose ingredients, potential contaminants, and drug interactions; requiring third-party testing for contaminants before products are sold; and implementing Good Manufacturing Practices (GMP) to ensure clean and controlled production environments. Without more rigorous regulatory oversight and clinical validation, nutraceuticals will remain in a regulatory gray area, which could pose risks to public health [11,1].

Current Regulations for Nutraceuticals

Safety and Toxicological Assessment: Although these nutraceuticals are promoted for their benefits to overall well-being, their bioactive constituents may pose serious

health risks if not properly evaluated. Therefore, a comprehensive toxicological and safety assessment framework is essential for consumer protection. The risk assessment process consists of four key steps: hazard identification, hazard characterization, exposure assessment, and risk characterization.

Hazard identification is the process of seeing whether a substance has the potential to cause any harm. This involves identifying any potentially toxic bioactive compounds, contaminants, or interactions that can pose health risks. These hazards can be caused by residues from agricultural chemicals, heavy metals, synthetic additives, or even adulteration during manufacturing. For instance, specific plant-based nutraceuticals have been found to contain pyrrolizidine alkaloids, which are known for their hepatotoxic potential. This step requires rigorous chemical analysis, such as mass spectrometry, and toxicology literature reviews, as well as, when necessary, in vivo and in vitro studies to define the toxicity profile for each component of a nutraceutical. Core toxicological tests in this phase often include LD_{50} studies to determine the median lethal dose, mutagenicity assays (such as the Ames test) to assess genetic damage potential, and 90-day subchronic toxicity studies to evaluate long-term safety in animal models.

Hazard characterization examines the nature and magnitude of any adverse effects that can result from the identified hazards. It includes dose-response assessment and toxicological profiling to define safe intake limits. The severity of outcomes could range from mild discomfort to organ toxicity, including neurotoxicity, hepatotoxicity, immunotoxicity, allergenicity, or cancer. Multiple studies, including animal studies, human epidemiological data, and in vitro assays, help define the NOAEL (No Observed Adverse Effect Level) and LOAEL (Lowest Observed Adverse Effect Level) values. For instance, the carcinogenic potential of benzophenone compounds used in food packages is tested through genotoxicity studies. Safety margins and uncertainty factors are used to account for any variability that may exist and ensure public safety [2]. Additionally, many nutraceuticals seek Generally Recognized As Safe (GRAS) status, which requires expert consensus and supporting safety data to affirm that a substance is safe under intended use conditions. GRAS designation plays a crucial role in guiding product formulation and market approval.

The third step, exposure assessment, estimates the amount, frequency, and duration of exposure to the previously identified hazard. This is where the quantity of the bioactive compound consumed, its frequency, and the identity of the consumer are quantified. It examines various patterns of consumption, including dietary habits of the population, age groups, metabolic differences, and health conditions. For instance, elderly individuals or those with compromised liver or kidney function may metabolize certain compounds differently, which can increase their susceptibility to certain toxic compounds. Product formulation also matters, particularly in terms of active compound concentration and batch-to-batch variability. Exposure can occur primarily through ingestion but may also happen dermally or via inhalation in certain supplement forms. Special populations, including children and those on medications, may also have significantly different exposure profiles. This assessment utilizes dietary intake surveys, pharmacokinetic modeling, and biomonitoring data to establish precise exposure scenarios. They also pay close attention to active compounds in different formulations, as there is a significant range and variability between various brands and batches that can alter exposure levels [2].

Risk characterization is the final and integrative step of the risk assessment process. It combines findings from the first three steps to estimate the likelihood and the severity of adverse effects that occur under realistic exposure conditions. The phase assesses the probability

that a given level of exposure will lead to harmful outcomes in sensitive subgroups. Ranking systems are used to visualize and prioritize risks; for instance, the threat of heavy metal contamination in herbal supplements is a higher priority than the variability in probiotic efficacy. Risk characterization also includes an uncertainty analysis to quantify confidence in the results and highlight factors with the most significant influence on these outcomes. These assessments inform regulatory decisions, such as setting permissible exposure limits, revising labeling requirements, or imposing bans or reformulations. Clear communication of these risks is vital to ensure consumer awareness and support the responsible production and use of nutraceuticals.

Overall, a scientifically rigorous risk assessment is essential to ensure the safety of consumers when ingesting nutraceuticals. While these products offer promising health benefits, they may be compromised when not handled with care and precision [2]. Without more rigorous regulatory monitoring and clinical validation, nutraceuticals will continue to operate in a regulatory gray area, which could endanger public health [11,1].

Global Regulatory Concerns: The regulation of nutraceuticals has remained a complex issue, largely because there is no internationally accepted definition. The Codex Alimentarius, developed by the World Health Organization (WHO) and the United Nations Food and Agriculture Organization (UNFAO), has become an international guideline to provide a basic standard for food safety, including nutraceuticals. However, it still doesn't offer a clear regulatory framework, which makes it difficult to have consistent global regulation of nutraceuticals.

In the United States, the Dietary Supplement Health and Education Act (DSHEA) of 1994 allows manufacturers to sell nutraceuticals without prior FDA approval, if they don't make explicit claims about treating diseases with their products [52]. In contrast, the European Food Safety Authority (EFSA) requires companies to get approval for any health claims made on nutraceutical packaging. This approval process includes a thorough analysis of scientific evidence supporting the claim. However, despite being more stringent than the US, Europe still does not officially define the term "nutraceutical," leaving these products under the same category as food supplements, functional foods, or medicinal foods, depending on the product's composition [52].

In other regions, such as Canada and Japan, nutraceuticals are regulated more strictly than in the U.S. but more leniently than in Europe. In Canada, nutraceuticals are treated as Natural Health Products, requiring manufacturers to obtain a product license that demonstrates safety, quality, and efficacy. Similarly, Japan classifies many nutraceuticals under its FOSHU category, requiring government approval before products can be marketed with specific health claims [49].

To overcome the risks, regulatory bodies such as the FDA and WHO must implement stricter safety regulations for nutraceuticals. This entails implementing stronger labeling regulations that require complete disclosure of ingredients, potential contaminants, and potential drug interactions. Additionally, third-party testing for contaminants should be required before products reach the market. Good Manufacturing Practices should also be enforced to ensure clean and controlled production environments.

CONCLUSION

The evolution of Ayurveda into nutraceuticals reflects a scientific shift in how we understand and pursue health. Nutraceuticals extend beyond the frameworks of modern medicine by embracing a preventative, holistic philosophy that's rooted in using nature to its benefit. By drawing on Ayurvedic principles, such as dosha balance

and Prakrit, and aligning them with modern insights into epigenetics, along with increasingly prominent health issues like metabolic diseases, cancer, and neurodegenerative diseases, nutraceuticals offer a personalized approach to disease management that resonates with both ancient knowledge and current biomedical evidence.

Nutraceuticals provide individuals with the option to use accessible, natural supplements as a preventive and therapeutic intervention. As the lines between nutraceuticals and medicine blur, nutraceuticals offer a promising path forward. Incorporating standard toxicological testing protocols, including LD_{50}, 90-day subchronic, and mutagenicity studies, along with GRAS certification processes, is fundamental to establishing a strong foundation for public health safety and regulatory acceptance.

List of Abbreviations: body mass index (BMI), basal metabolic rate (BMR), messenger RNA (mRNA), transfer RNA**.** (tRNA), Ayurveda, Yoga & Naturopathy, Unani, Siddha, and Homeopathy Ministry (AYUSH), cardiovascular diseases (CVD), compound annual growth rate (CAGR), Foods for Specified Health Use (FOSHU), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), Alzheimer's disease (AD), Parkinson's disease (PD), epigallocatechin gallate (EGCG), , hypothalamic-pituitary-adrenal (HPA), gamma-aminobutyric acid (GABA), N-Methyl-D-Aspartate (NMDA), nitric oxide (NO), cancer stem cells (CSCs), bergamot extract (BEO), natural killer (NK), gut-associated lymphoid tissue (GALT), Toll- like receptors (TLR), World Health Organization (WHO), European Food Safety Authority (EFSA), NOAEL (No Observed Adverse Effect Level) and LOAEL (Lowest Observed Adverse Effect Level), Generally Recognized As Safe (GRAS).

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