



Mito-Nutraceutical Potential of Plant Secondary Metabolites

Subramani Paranthaman Balasubramani*, Skyler A. Armstead, Adreanna T. Buggs, Myla S. Bell

Abstract

Mitochondria, the cellular powerhouses, are essential for energy production and various metabolic processes. This review explores the potential of plant secondary metabolites (PSMs) as nutraceuticals to modulate mitochondrial structure and function. Mitochondrial dynamics, including fission, fusion, biogenesis, and mitophagy, are crucial for maintaining cellular homeostasis. Dysregulation of these processes is linked to diseases such as neurodegenerative disorders, metabolic syndromes, cancer and aging. PSMs, including polyphenols, alkaloids, terpenoids, and flavonoids, form a part of our nutrition and can influence mitochondrial function through multiple pathways. PSMs enhance mitochondrial efficiency, stimulate biogenesis, and reduce oxidative stress by activating key signaling pathways like AMP-activated protein kinase (AMPK), sirtuins, and nuclear factor erythroid 2-related factor 2 (Nrf2). These compounds also stabilize mitochondrial membranes, protect against oxidative damage, and support mitochondrial quality control mechanisms. By modulating mitochondrial dynamics and reducing oxidative stress, PSMs offer promising avenues for improving metabolic health and combating degenerative diseases. However, challenges such as variability in PSM content, dosage for targeted delivery and interactions with other dietary components must be addressed. Future research should focus on developing targeted delivery systems, such as PSM-loaded nanoparticles, to enhance bioavailability and to maximize therapeutic efficacy. In summary, PSMs represent a valuable resource for mitochondrial therapeutics, with the potential to revolutionize approaches to health and disease management. Understanding the molecular mechanisms by which PSMs modulate mitochondrial function can lead to innovative strategies for enhancing cellular resilience and metabolic efficiency.

Keywords: Plant Secondary Metabolites; Nutraceuticals; Mitochondrial dynamics; Aging; Chronic diseases; Nanoparticles

Introduction

Mitochondria, often referred to as the "powerhouses of the cell," are vital cellular organelles found in nearly all eukaryotic organisms. These tiny, double-membraned structures play a central role in cellular energy production by generating adenosine triphosphate (ATP), the primary energy currency of the cell. Their presence is crucial for a variety of metabolic processes that sustain life, from muscle contraction to cell division and beyond. Structurally, mitochondria are characterized by an outer membrane that encapsulates the organelle and an intricately folded inner membrane, forming structures called cristae. These cristae increase the surface area available for chemical reactions, particularly those involved in the electron transport chain and oxidative phosphorylation, the processes that drive ATP production. The matrix, the

Affiliation:

Department of Natural Sciences, Albany State University, Albany, GA 31705 USA

*Corresponding author:

Subramani Paranthaman Balasubramani, Department of Natural Sciences, Albany State University, Albany, GA 31705 USA

Citation: Subramani Paranthaman Balasubramani, Skyler A. Armstead, Adreanna T. Buggs, Myla S. Bell. Mito-Nutraceutical Potential of Plant Secondary Metabolites Fortune Journal of Health Sciences, 8 (2025): 217-244.

Received: February 22, 2025

Accepted: March 03, 2025

Published: March 20, 2025

innermost compartment, houses enzymes, mitochondrial DNA (mtDNA), and ribosomes, enabling mitochondria to produce some of their own proteins.

Interestingly, mitochondria are unique among organelles because they possess their own DNA, inherited maternally, and are capable of reproducing independently within the cell. This autonomy hints at their evolutionary origins as free-living prokaryotes that entered into a symbiotic relationship with ancestral eukaryotic cells. This theory, known as the endosymbiotic theory, explains their distinct genetic and structural characteristics. Beyond energy production, mitochondria are involved in various essential cellular functions. They regulate calcium signaling, contribute to the synthesis of certain biomolecules, and play a pivotal role in programmed cell death, or apoptosis, which is crucial for development and disease prevention [1]. Understanding mitochondria is fundamental to exploring health and disease, as mitochondrial dysfunction has been implicated in a range of conditions, from neurodegenerative disorders like Parkinson's and Alzheimer's to metabolic syndromes and aging [2]. This multifaceted organelle continues to captivate researchers, underscoring its importance in biology and medicine.

Mitochondrial Dynamics: A Balancing Act of Cellular Life

Mitochondrial dynamics encompass the processes of fission, fusion, biogenesis, and mitophagy, which collectively maintain mitochondrial structure, function, and distribution [2]. These dynamic processes are essential for cellular homeostasis, enabling mitochondria to adapt to physiological demands, repair damage, and respond to stress. Their balance is crucial for health, and dysregulation is implicated in various diseases [3, 4, 5]. Fusion allows mitochondria to merge, forming networks that enhance their functional capacity and facilitate the exchange of mitochondrial DNA, proteins, and metabolites. This process mitigates the effects of mitochondrial DNA mutations and ensures the uniform distribution of metabolic components. Key proteins involved in fusion include mitofusins (Mfn1, Mfn2) on the outer membrane and optic atrophy protein 1 (OPA1) on the inner membrane [6]. Fission, conversely, enables mitochondrial division, critical for proper distribution during cell division, isolation of damaged regions, and mitophagy. The protein dynamin-related protein 1 (Drp1) orchestrates fission by recruiting to mitochondrial sites to mediate division. Disruptions in the balance of fusion and fission can lead to dysfunctional mitochondrial networks, impairing cellular function [6].

Biogenesis, regulated by the master activator PGC-1 α , ensures the formation of new mitochondria to meet energy demands and replace damaged ones. It involves the replication

of mitochondrial DNA, synthesis of proteins, and integration of lipids [4]. Mitophagy, a quality control mechanism, eliminates dysfunctional mitochondria. Proteins such as PINK1 and Parkin signal for the autophagic degradation of damaged organelles, preventing the accumulation of reactive oxygen species (ROS) and inflammation [7]. Impaired mitochondrial dynamics contribute to neurodegenerative diseases, metabolic syndromes, cardiovascular disorders, and aging [6]. Targeting the proteins involved in these processes offers therapeutic potential for correcting mitochondrial dysfunction. Mitochondrial dynamics represent a finely tuned regulatory system critical to cellular health and disease intervention strategies.

The Role of Mitochondria In Aging And Degenerative Diseases

Mitochondria are central to aging, degenerative diseases, and cancer progression due to their roles in energy production, cellular homeostasis, and oxidative stress regulation. Aging is associated with mitochondrial dysfunction, characterized by reduced ATP production, increased reactive oxygen species (ROS), and mitochondrial DNA (mtDNA) mutations [8]. This contributes to cellular damage, tissue dysfunction, and age-related diseases. Oxidative stress, driven by excess ROS, damages proteins, lipids, and DNA, creating a cycle of mitochondrial damage and ROS production that accelerates aging and increases vulnerability to degenerative conditions [7, 9]. Mitochondrial dysfunction is a hallmark of neurodegenerative diseases, such as Alzheimer's and Parkinson's, where impaired mitophagy, mitochondrial fragmentation, and defective energy metabolism lead to neuronal death [2, 7].

For example, mutations in PINK1 and Parkin, key regulators of mitophagy, are linked to mitochondrial accumulation in Parkinson's disease. Similarly, metabolic syndromes, cardiovascular diseases, and sarcopenia are associated with mitochondrial dysfunction in aging [2, 10]. Therapies targeting mitophagy, mitochondrial biogenesis, and ROS reduction are being explored to slow aging and mitigate degenerative diseases. In cancer, mitochondria play a multifaceted role by supporting energy metabolism, signaling, and cell survival. Cancer cells exhibit metabolic reprogramming, often shifting to aerobic glycolysis (Warburg effect) while retaining mitochondrial activity to sustain ATP production and biosynthesis [3, 4]. Mitochondria also produce ROS, which at moderate levels promote genetic instability, survival, and angiogenesis [2]. Cancer cells balance ROS by upregulating antioxidant systems [8, 11]. Mitochondria regulate apoptosis, but cancer cells evade this by altering mitochondrial pathways, such as overexpressing anti-apoptotic proteins like Bcl-2 [11]. Altered mitochondrial dynamics, including fusion, fission, and mitophagy, enhance

adaptability, drug resistance, and metastasis. Targeting mitochondrial metabolism, ROS regulation, and dynamics holds therapeutic potential for aging-related diseases and cancer, offering new avenues for intervention [8].

Nutritional Factors Impacting Mitochondrial Structure And Function

Nutritional factors significantly influence mitochondrial structure and function, shaping cellular energy production, oxidative stress management, and overall metabolic health [12]. The quality and quantity of nutrients can directly affect mitochondrial biogenesis, dynamics, and efficiency, impacting health and susceptibility to disease [13]. Macronutrients such as carbohydrates, fats, and proteins are primary sources of substrates for mitochondrial energy production through oxidative phosphorylation. An excess of nutrients, particularly fats and refined carbohydrates, can lead to mitochondrial overload, promoting the production of ROS and impairing mitochondrial function [14, 15]. Conversely, caloric restriction or intermittent fasting has been shown to enhance mitochondrial efficiency, stimulate biogenesis, and reduce oxidative stress [16]. Micronutrients are also essential for mitochondrial function. Vitamins like B-complex (e.g., B1, B2, B3, and B5) are cofactors in key mitochondrial enzymes, while minerals such as magnesium and iron are crucial for ATP synthesis and electron transport chain activity [17].

Deficiencies in these nutrients can impair mitochondrial energy production and increase susceptibility to dysfunction. Antioxidants, including vitamins C and E, and compounds like coenzyme Q10 and polyphenols, play a protective role by neutralizing excess ROS and preventing oxidative damage to mitochondrial membranes, proteins, and DNA [18]. Diets rich in fruits, vegetables, and antioxidant compounds

can support mitochondrial health. Omega-3 fatty acids, found in fish oil, enhance mitochondrial membrane fluidity and function, improving energy efficiency and reducing inflammation. In contrast, excessive intake of saturated and trans fats can impair membrane integrity and promote dysfunction [13]. Plant-derived bioactive compounds, such as resveratrol and curcumin, can activate signaling pathways like AMP-activated protein kinase (AMPK) and sirtuins, promoting mitochondrial biogenesis and resistance to stress [19]. Balanced nutrition, rich in essential micronutrients, antioxidants, and healthy fats, supports mitochondrial health, while overnutrition or deficiencies can impair structure and function, contributing to metabolic and degenerative diseases.

Plant Secondary Metabolites and Their Impact on Mitochondrial Structure and Function

Plant secondary metabolites (PSMs) are bioactive compounds produced by plants that serve various ecological functions, such as defense against herbivores and pathogens. These compounds, including polyphenols, alkaloids, terpenoids, and flavonoids, have significant impacts on mitochondrial structure and function in human cells, influencing energy production, oxidative stress, and cellular signaling pathways. Figure 1 gives a brief classification of different types of nutrients provided by plant foods with a special emphasis on secondary metabolites. Polyphenols, such as resveratrol, quercetin, and catechins, are among the most studied PSMs. They modulate mitochondrial function by enhancing oxidative phosphorylation efficiency, stimulating mitochondrial biogenesis through pathways like AMP-activated protein kinase (AMPK) and sirtuins, and reducing reactive oxygen species (ROS) levels. Polyphenols also stabilize mitochondrial membranes, protecting against damage induced by oxidative stress [20].

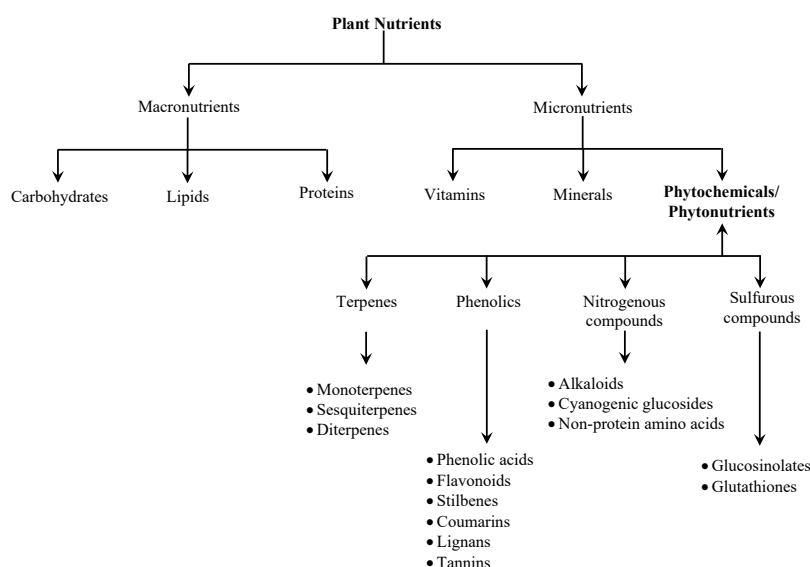
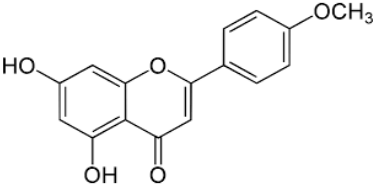
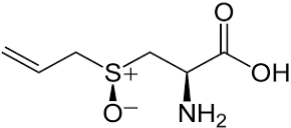
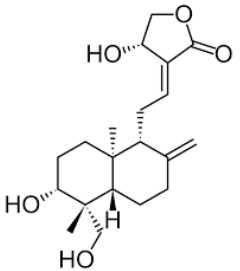
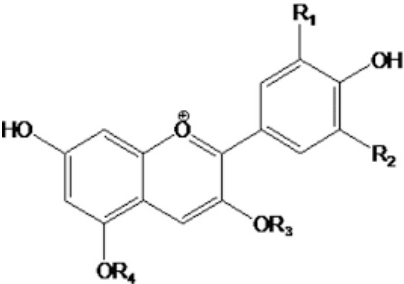


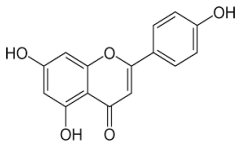
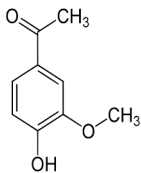
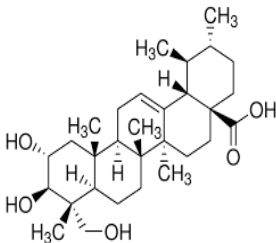
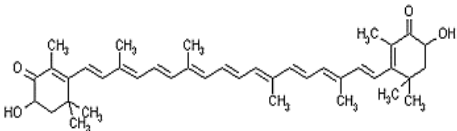
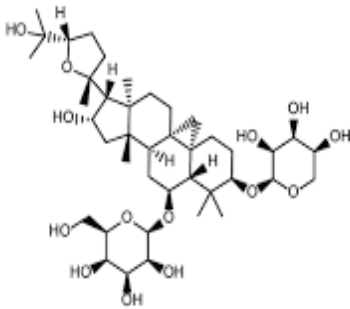
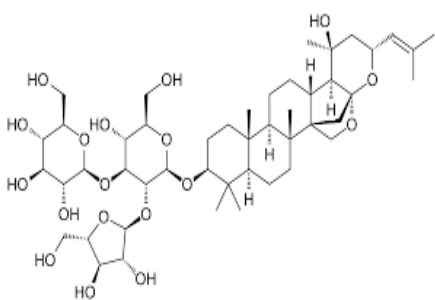
Figure 1: Classification of phytonutrients with an emphasis on plant secondary metabolites (PSM)

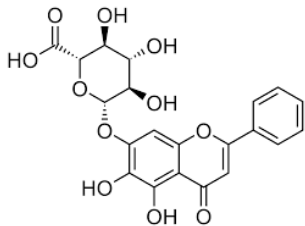
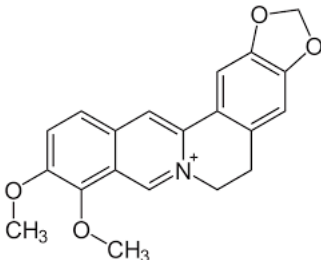
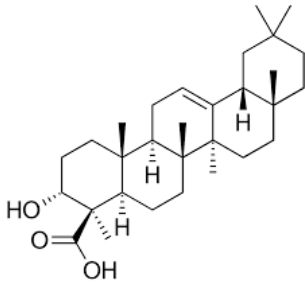
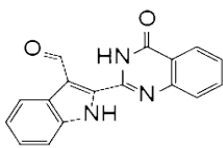
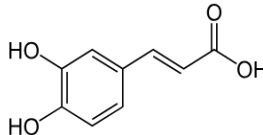
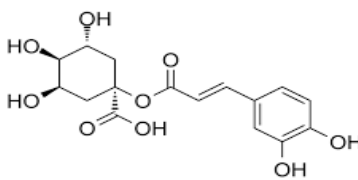
Alkaloids, including berberine, have demonstrated the ability to regulate mitochondrial energy metabolism. Berberine, for instance, improves mitochondrial function by activating AMPK, thereby enhancing energy efficiency and reducing mitochondrial dysfunction in metabolic disorders [21]. Terpenoids, such as carotenoids and ginsenosides, support mitochondrial health by protecting against oxidative damage and modulating mitochondrial dynamics [20, 22]. Carotenoids, for example, enhance mitochondrial membrane integrity and reduce ROS production, while ginsenosides promote mitochondrial energy production and biogenesis [23]. Flavonoids, such as hesperidin and kaempferol, impact mitochondrial function by modulating apoptosis, reducing oxidative damage, and supporting mitochondrial DNA

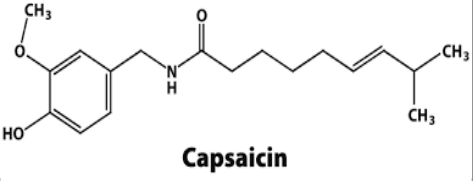
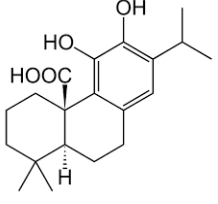
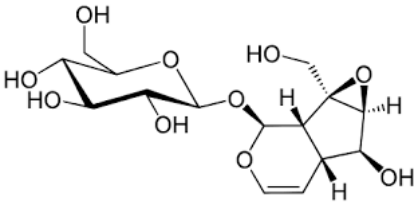
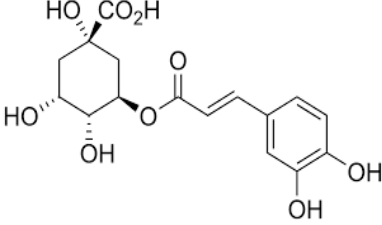
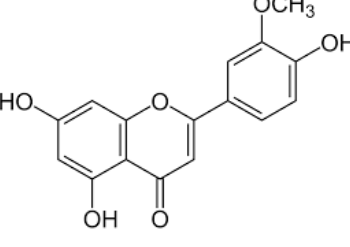
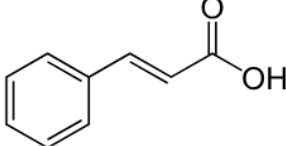
integrity [24]. These effects are particularly valuable in mitigating age-related mitochondrial decline and preventing degenerative diseases. Additionally, some PSMs exhibit protective effects against mitochondrial dysfunction associated with diseases. For instance, curcumin and epigallocatechin gallate (EGCG) have shown potential in reducing mitochondrial damage in neurodegenerative and metabolic disorders by improving antioxidant defenses and enhancing mitochondrial quality control mechanisms, such as mitophagy [25, 26]. In summary, plant secondary metabolites profoundly influence mitochondrial structure and function by enhancing energy efficiency, reducing oxidative stress, and protecting against dysfunction. Their potential therapeutic applications offer promising avenues for improving metabolic health and combating mitochondrial-related diseases.

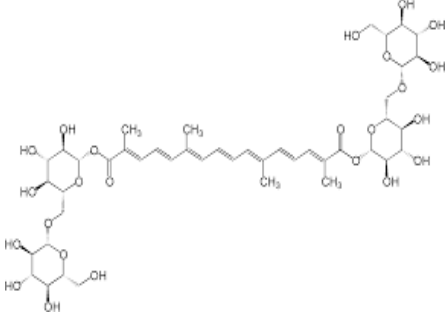
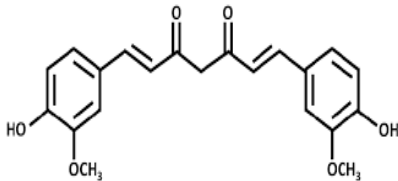
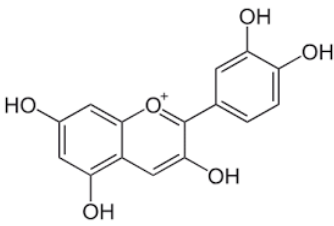
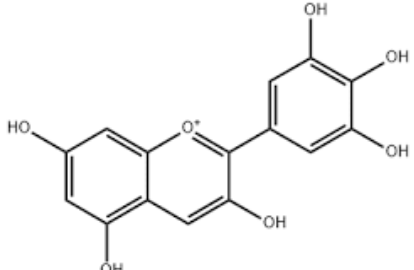
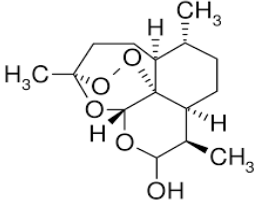
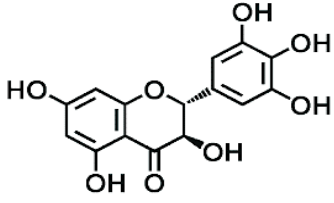
Table 1: List of PSMs identified to have mitochondrial dynamics and function modulating potential

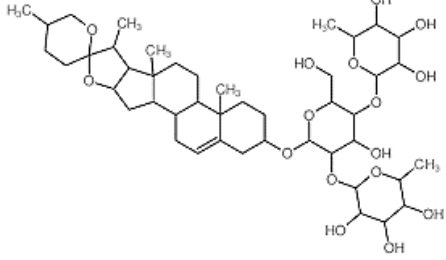
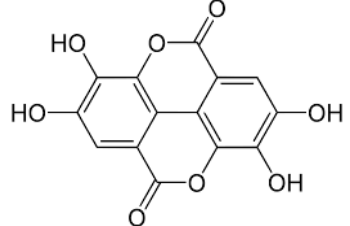
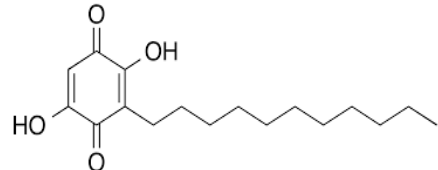
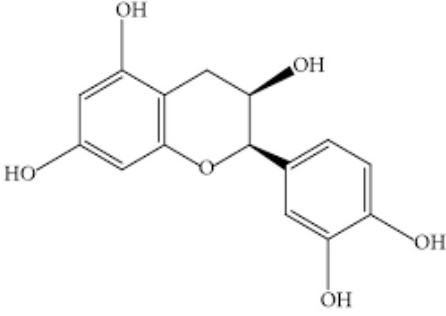
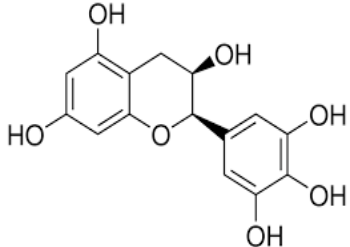
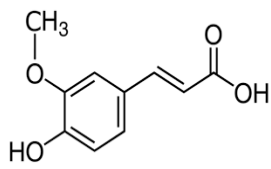
Secondary Metabolite	Chemical Formula	Chemical structure	Source of compound	Function
Acacetin	C ₁₆ H ₁₂ O ₅		Black locust, Damiana, Silver birch, Rainforest spleenwort	Mitophagy
Allin	C ₆ H ₁₁ NO ₃ S		Garlic	Mitophagy
Andrographolide	C ₂₀ H ₃₀ O ₅		Bitter weed	Antioxidant, Mitochondrial integrity, Mitophagy
Anthocyanin	C ₁₅ H ₁₁ O ⁺		Strawberries, Blueberry, Raspberry, Black rice, and Black soybean, among many others that are red, blue, purple, or black.	Basal respiration

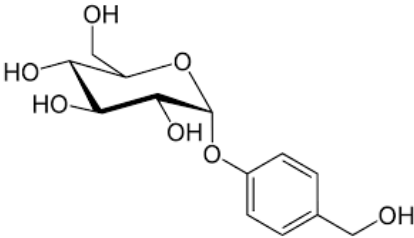
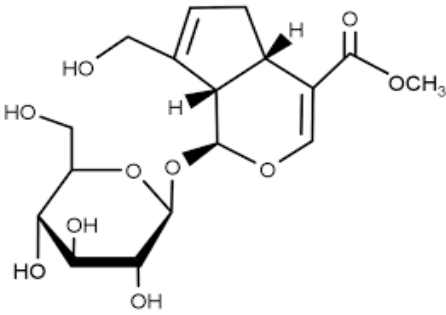
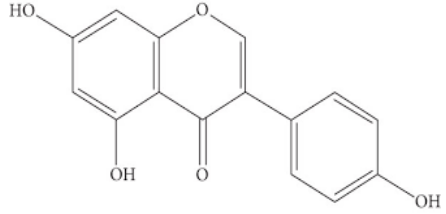
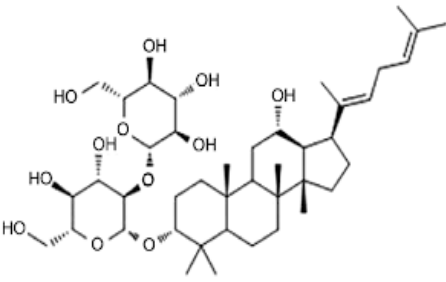
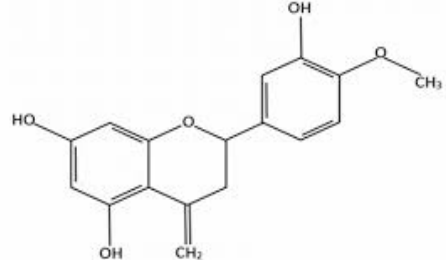
Apigenin	C ₁₅ H ₁₀ O ₅		Parsley, Celery, Celeriac, and Chamomile tea	Mitochondrial energetics
Apocynin	C ₉ H ₁₀ O ₃		Dogbane and Kutki	Respiration
Asiatic acid	C ₃₀ H ₄₈ O ₅		Gotu kola plant, Hardy kiwi, Dune Koko tree, Guava, Chilean guava berry, and Craibiodendron	Mitochondrial dynamics, ATP generation
Astaxanthin	C ₄₀ H ₅₂ O ₄		Adonis plants	Antioxidant
Astragaloside IV	C ₄₁ H ₆₈ O ₁₄		Mongolian milkvetch	Antioxidant, ETC activity, Mitochondrial regeneration
Bacosides and Bacopasides	C ₄₁ H ₆₈ O ₁₃ & C ₄₇ H ₇₆ O ₁₈		Water hyssop	Respiration, Mitochondrial regeneration

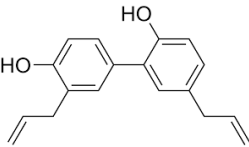
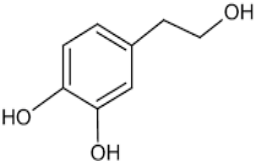
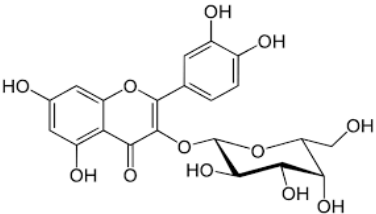
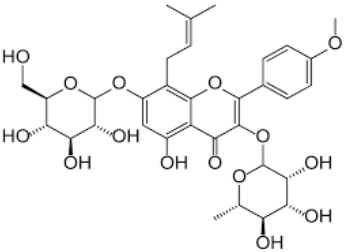
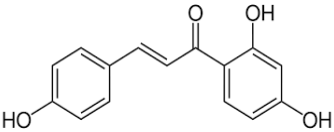
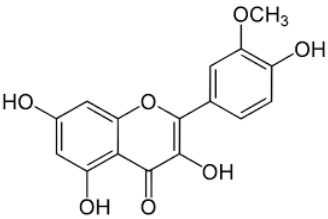
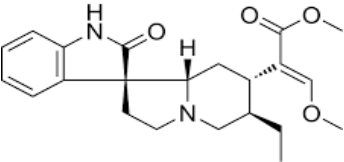
Baicalin	C ₂₁ H ₁₈ O ₁₁		Chinese skullcap, Blue skullcap in marsh skullcap, and Indian trumpet tree	Optimize mitochondrial regeneration, Antioxidant
Berberine	C ₂₀ H ₁₈ NO ₄ ⁺		Barberry, Tree turmeric, Oregon grape, Goldenseal, yellow-root, Amur cork tree, Chinese goldthread, Prickly poppy, California poppy	Mitophagy, Antioxidant, SIRT3 activation, ATP generation, Mitochondrial integrity
Boswellic acids	C ₃₀ H ₄₈ O ₃		Indian Frankincense	Mitochondrial respiration
Bouchardatine	C ₂₂ H ₁₉ N ₃ O ₂	 Bouchardatine	Union nut plant	Mitochondrial biogenesis
Caffeic acid	C ₉ H ₈ O ₄		Apples, Artichokes, Berries, Pears Thyme, Sage, Turmeric, and Eucalyptus	Antioxidant, Modulate mitochondrial dynamics
Caffeoylquinic acid derivatives	C ₁₆ H ₁₈ O ₉		Sweet potatoes, Coffee bean,	Respiration, Fatty acid oxidation

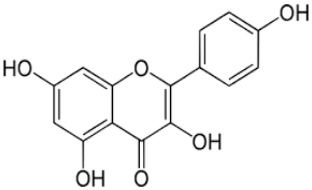
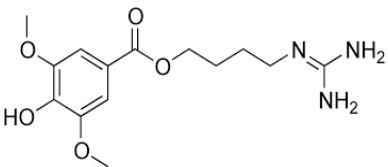
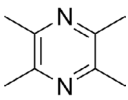
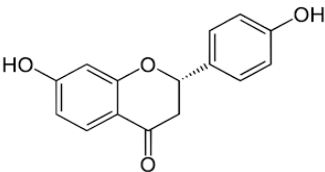
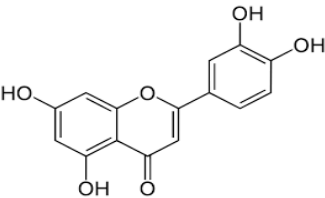
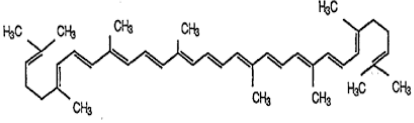
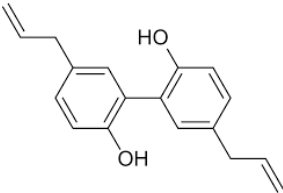
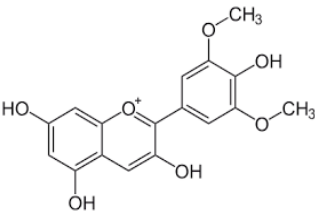
Capsaicin	C ₁₈ H ₂₇ NO ₃	 <p>Capsaicin</p>	Chili pepper	Antioxidant, Ionic balance
Carnosic acid	C ₂₀ H ₂₈ O		Rosemary and Common sage	Antioxidant, Mitochondrial dynamics, Respiration
Catalpol	C ₁₅ H ₂₂ O ₁₀		<i>Rehmannia glutiosa</i> ,	Enhanced ATP and membrane potential, improved mitochondrial dynamics
Chlorogenic acid	C ₁₆ H ₁₈ O ₉		Sweet potatoes, Green coffee beans, Apples, pears, Berries, carrots, Potatoes, Tomatoes, and Eggplants, Artichoke, Betel, Burdock, Wormwood, and Rosemary, Honeysuckle, Eucommia, Tobacco leaves, and Mulberry leaves.	Fatty acid oxidation, Antioxidant
Chrysoeriol	C ₁₆ H ₁₂ O ₆		Artemisia	Suppress protein processing
Cinnamic acid	C ₉ H ₈ O ₂		Spinach, Cinnamon, Citrus fruits, Wheat	Fatty acid oxidation, Antioxidant

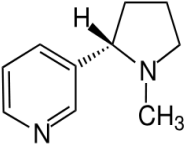
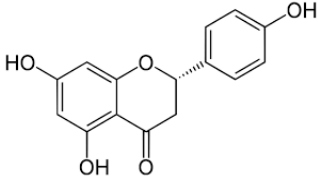
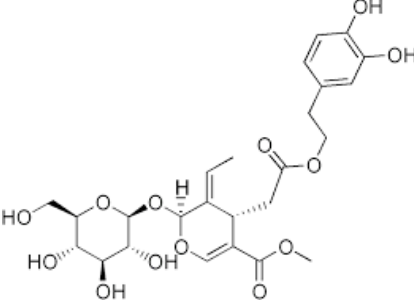
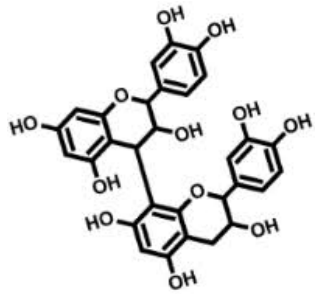
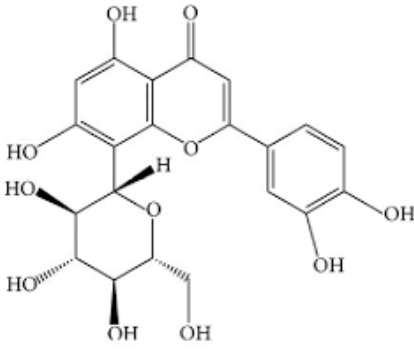
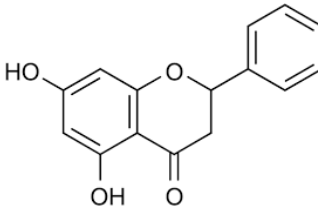
Crocin	C ₄₄ H ₆₄ O ₂₄		Saffron, flowers of Crocus and Gardenia	Respiration
Curcumin	C ₂₁ H ₂₀ O ₆		Turmeric	Mitophagy, modulate antioxidant activity, Membrane potential
Cyanidin	C ₁₅ H ₁₁ O ₆ ⁺		Red-fleshed apples, Bilberries, Cranberries, Chokeberries, Grapes, Hawthorn, Lingonberries, Loganberries, Raspberries, Açai berries, Red cabbage and Red onions	Antioxidant, Mitochondrial dynamics
Delphinidin	C ₁₅ H ₁₁ O ₇ ⁺		Maqui berries, Cranberries, Concord grapes, Bilberries, Strawberries, Blueberries, Blackberries, Blackcurrant, Redcurrant, Raspberries, Eggplant, Roselle, and Wine.	Respiration
Dihydroartemisinin	C ₁₅ H ₂₄ O ₅		Sweet wormwood plant, and Artemisia annua	Ionic balance
Dihydromyricetin	C ₁₅ H ₁₂ O ₈		Vine tea, Oriental raisin tree, Deodar cedar, Moyeam, Katsura tree, and Japanese fantail willow	Antioxidant, Mitochondrial biogenesis, Mitochondrial gene expression

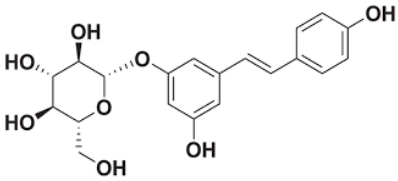
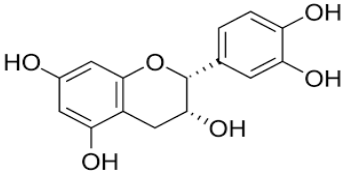
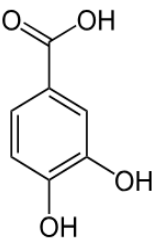
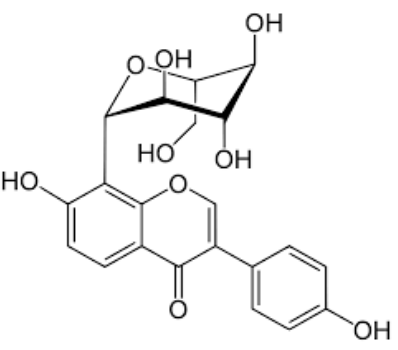
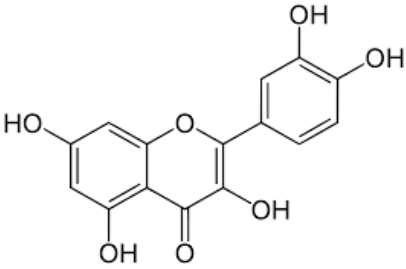
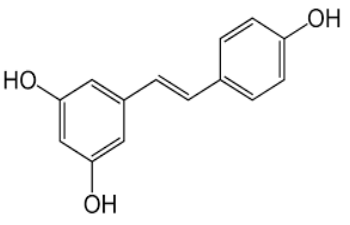
Dioscin	C ₂₇ H ₄₂ O ₃		Wild yam, Fenugreek, Yam, Himalayan trillium, Ginger, Smilax china, and <i>Rhizoma polygonati</i>	Antioxidant, Mitochondrial integrity
Ellagic acid	C ₁₄ H ₆ O ₈		Goji berries, Blackberries, Raspberries, Strawberries, and Cranberries	Antioxidant, Mitochondrial regeneration
Embelin	C ₁₇ H ₂₆ O		Berries of the <i>Embelia ribes</i> plant	Mitochondrial biogenesis
Epicatechin	C ₁₅ H ₁₄ O ₆		Cocoa beans, Tea, Grapes	Respiration, Antioxidant, Mitophagy
Epigallocatechin-3-gallate	C ₂₁ H ₂₂ O ₁₃		Tea and Cocoa beans	Respiration, Mitochondrial biogenesis
Ferulic acid	C ₁₀ H ₁₀ O ₄		Rice, Oats, Wheat, Oranges, Apples	Ionic balance, maintain mitochondrial integrity, Antioxidant

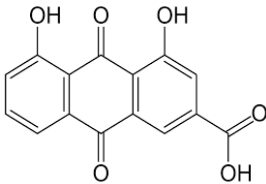
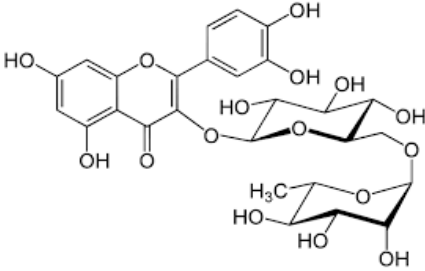
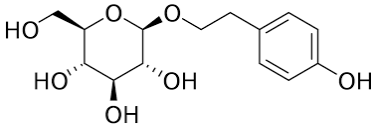
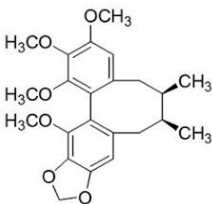
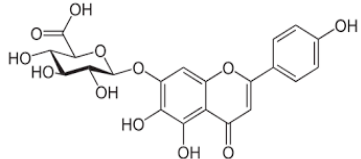
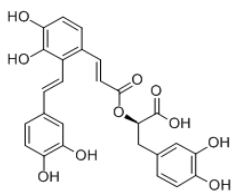
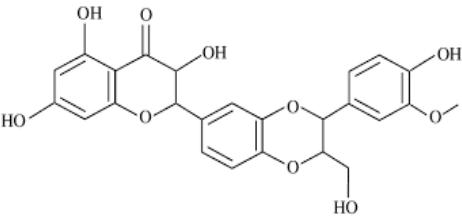
Gastrodin	C ₁₃ H ₁₈ O ₇		<i>Gastordia elata</i>	Antioxidant, Respiration
Geniposide	C ₁₇ H ₂₄ O ₁₀		<i>Gardenia jasminoids</i>	Ionic balance
Genistein	C ₁₅ H ₁₀ O ₅		Soybeans	Respiration, Mitochondrial integrity
Ginsenoside Rg5	C ₄₂ H ₇₀ O ₁₂		Gardenia Jasminoids, Hardy Rubber tree, Chinese Foxglove, Beverly Bells flower, Xuan Shen, and Figwort plant	Mitochondrial integrity, Energy metabolism, Antioxidant
Hesperidin	C ₂₈ H ₃₄ O ₁₅		Oranges and Lemons	Antioxidant, ATP production, Modulating membrane potential

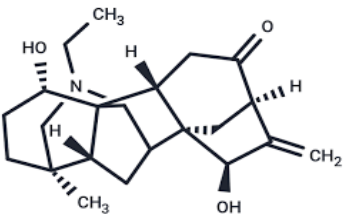
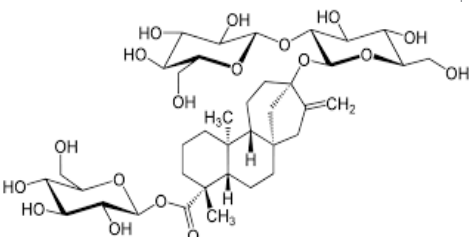
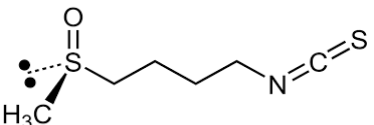
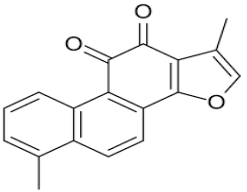
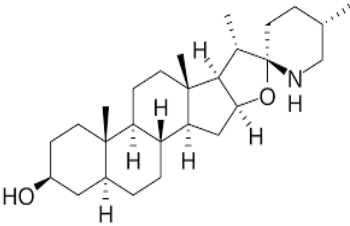
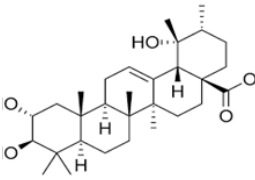
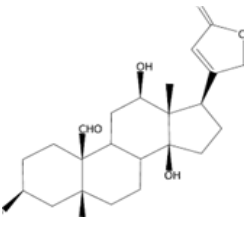
Honokiol	C ₁₈ H ₁₈ O ₂		Magnolia tree	Respiration, Enhance ATP production, Antioxidant, Mitochondrial regeneration
Hydroxytyrosol	C ₈ H ₁₀ O ₃		Olive leaves and oil	Respiration, Antioxidant, Mitochondrial dynamics
Hyperoside	C ₂₁ H ₂₀ O ₁₂		Mountain Hawthorn Plant Weeping Forsythia Shrub, Holoparasite vine, Perennial Shrub/Flower Tree, Deadnettle, Sage, Rhododendron, and Aconitaceae, Garcinia	Mitochondrial regeneration, Fission
Icariin	C ₃₃ H ₄₀ O ₁₅		Horny Goat Weed	Improve mitochondrial dynamics and integrity
Isoliquiritigenin	C ₁₅ H ₁₂ O ₄		Roots of licorice family	Antioxidant, Modulate AMP/ATP ratio
Isorhamnetin	C ₁₆ H ₁₂ O ₇		Red turnip, Goldenrod, Mustard Leaf, Almonds, Chives, Dill Weed, Fennel Leaves, and Ginkgo Biloba	Antioxidant
Isorhynchophylline	C ₂₂ H ₂₈ N ₂ O ₄		Gou-Teng and Gambier	Mitochondrial degeneration

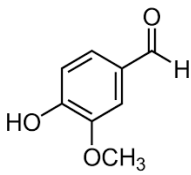
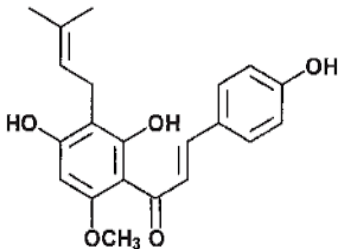
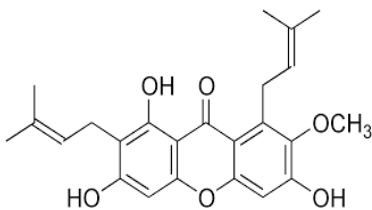
Kaempferol	C ₁₅ H ₁₀ O ₆		Spinach, Kale, Broccoli Sap and Berries	Antioxidant, Mitophagy, Ca uptake
Leonurine	C ₁₄ H ₂₁ N ₃ O ₅		Plant Herba Leonuri, Lion's ear, and Lion's tail	Modulate mitochondrial activity
Ligustrazine	C ₈ H ₁₂ N ₂		Chuanxiong	Membrane potential
Liquiritigenin	C ₁₅ H ₁₂ O ₄		Licorice, Jacaranda Obtusifolia Flower, Indian Kino Tree	Mitochondrial integrity
Luteolin	C ₁₅ H ₁₀ O ₆		Clover blossoms, Rosemary, Oregano, Parsley, Basil, Mint, Celery, Broccoli, Artichoke, Oranges	Mitochondrial permeability, Antioxidant, Mitophagy
Lycopene	C ₄₀ H ₅₆		Watermelon, Tomatoes, Grapefruit, Papaya, Mangoes	Antioxidant, Structural integrity
Magnolol	C ₁₈ H ₁₈ O ₂		<i>Houpu magnolia</i> and in <i>M. grandiflora</i>	Inhibit respiration
Malvidin	C ₁₇ H ₁₅ O ₇ ⁺		Blueberries, Grapes, Black berries, Raspberries, Soybean	Basal respiration, Antioxidant, Mitochondrial dynamics

Naringenin	C ₁₅ H ₁₂ O ₅		Tomatoes, Grapefruit, Citrus fruits	Antioxidant, Mitophagy, Respiration
Nicotine	C ₁₀ H ₁₄ N ₂		Potatoes, Eggplants, Bell peppers and Tobacco leaves	Leaky mitochondria
Oleuropein	C ₂₅ H ₃₂ O ₁₃		Olive Tree	Antioxidant, Block protein processing
Oligonol	Mixture of polyphenols		Lychee fruits, Green Tea Extract	Mitochondrial biogenesis
Orientin	C ₂₁ H ₂₀ O ₁₁		Bamboo Leaves, Passion Flowers, <i>Ocimum Sanctum</i> , Acai Plum, Buckwheat Sprouts, Millets	Antioxidant, Mitochondrial integrity
Pinocembrin	C ₁₅ H ₁₂ O ₄		Pinus Heartwood, Eucalyptus, Populus, Euphorbia, Honey, Damiana	Mitochondrial dynamics

Polydatin	C ₂₀ H ₂₂ O ₈		Grape Skin	Antioxidant, improve mitochondrial membrane potential and integrity, Ca influx, ATP production
Procyanidin	C ₃₀ H ₂₆ O ₁₃		Grape seed, Apples, Cocoa beans, bark of Pine tree	Modulating mitochondrial protein profile, Antioxidant, Mitochondrial dynamics
Protocatechuic acid	C ₇ H ₆ O ₄		Plums, Gooseberries, Grapes, Nuts, and Almonds	Antioxidant, Mitochondrial integrity
Puerarin	C ₂₁ H ₂₀ O ₉		Kudzu plant	ATP production, Modulating mitochondrial fusion and fission, mitochondrial gene expression, antioxidant
Quercetin	C ₁₅ H ₁₀ O ₇		Berries, Cherries, Apples, Onions	Respiration, ATP production, ETC capacity, Mitophagy, Antioxidant
Resveratrol	C ₁₄ H ₁₂ O ₃		Grape, Almonds, Blue berries, Crane berries, Plum	Respiration, Fatty acid oxidation, Mitophagy, Antioxidant, Mitochondrial biogenesis

Rhein	C ₁₅ H ₈ O ₆		Rhubarb	Modulating membrane potential, ATP production, Enhancing mitochondrial dynamics
Rutin	C ₂₇ H ₃₀ O ₁₆		Buckwheat, Japanese Pagoda Tree, Eucalyptus, Lime Tree Flowers, Elder Flowers, Hawthorn, Rue, Ginko, Apples	Mitochondrial biogenesis, Antioxidant
Salidroside	C ₁₄ H ₂₀ O ₇		Rhodiola Plants	Autophagy
Salvianolic acid A/B	C ₃₆ H ₃₀ O ₁₆		Red sage	Restore mitochondrial membrane potential and integrity, Antioxidant, Modulate mitochondrial dynamics
Schisandrin	C ₂₄ H ₃₂ O ₇		Magnolia Vine	Ionic balance, antioxidant
Scutellarin	C ₂₁ H ₁₈ O ₁₂		Barbed Skullcap and Blue Skullcap	Mitochondrial biogenesis, Reduce lipid peroxidation, Antioxidant
Silibinin	C ₂₅ H ₂₂ O ₁₀		Milk Thistle	Improve mitochondrial dynamics, membrane potential

Songorine	C ₂₂ H ₃₁ NO ₃		Wolfsbane	Mitochondrial biogenesis
Stevioside	C ₃₈ H ₆₀ O ₁₈		Candy leaf	Ionic balance
Sulforaphene	C ₆ H ₉ NOS ₂		Cauliflower, Cabbage, Kale, and Bok choy	Mitophagy
Tanshinone IIA	C ₁₉ H ₁₈ O ₃		Dashen	Improve mitochondrial structure, Antioxidant
Tomatidine	C ₂₇ H ₄₅ NO ₂		Tomatoes	Mitophagy
Tormentric acid	C ₃₀ H ₄₈ O ₅		Olives, Strawberries, Mangos, Rose Fruits, Apples, Mulberry, Quince	Antioxidant, Mitochondrial integrity
Toxicarioside	C ₃₀ H ₄₄ O ₁₁		<i>Antiaris toxicaria</i> tree	Mitophagy

Vanillin	C ₈ H ₈ O ₃		Vanilla orchid	Antioxidant
Xanthohumol	C ₂₁ H ₂₂ O ₅		Female Inflorescences of <i>Humulus lupulus</i>	Promotes fusion
α-Mangostin	C ₂₄ H ₂₆ O ₆		Mangosteen	ATP synthesis, Membrane potential

Molecular Pathways Targeted By Psms to Modulate Mitochondrial Structure and Function

Plant secondary metabolites (PSMs) modulate mitochondrial structure and function through various molecular pathways, influencing energy production, oxidative stress management, and cellular signaling. These pathways involve direct interactions with mitochondrial components as well as regulation of key signaling cascades, which collectively enhance mitochondrial health and resilience. Table 1 provides a comprehensive list of PSMs identified to have mitochondrial structure and function modulating potential.

Plant Secondary Metabolites (PSM) Modulate the AMPK Pathway

Several PSMs have been identified to modulate the AMP-activated protein kinase (AMPK) pathway, a central regulator of cellular energy homeostasis. AMPK senses cellular energy levels by monitoring the AMP/ATP ratio and, when activated, promotes catabolic processes that generate ATP while suppressing energy-intensive anabolic pathways [27]. Through their interaction with the AMPK pathway, PSMs enhance mitochondrial function, support metabolic health, and provide protective effects against various diseases. Berberine and resveratrol has been shown to directly activate AMPK by influencing its upstream kinases, like liver kinase B1 (LKB1) and calcium/calmodulin-dependent protein kinase kinase 2 (CaMKK2). Berberine increases the AMP/ATP ratio, mimicking a low-energy state, which triggers LKB1-

mediated AMPK activation [21, 28]. Resveratrol, meanwhile, activates AMPK via mechanisms involving increased intracellular calcium, stimulating CaMKK2 [28]. Curcumin and catechins indirectly activate AMPK by reducing oxidative stress and improving mitochondrial function. For instance, curcumin enhances mitochondrial efficiency and reduces reactive oxygen species (ROS) levels, creating a favorable environment for AMPK activation. Through AMPK activation, PSMs stimulate the transcriptional coactivator PGC-1 α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha) [29]. PGC-1 α drives mitochondrial biogenesis by upregulating genes involved in mitochondrial replication and oxidative phosphorylation, thus improving energy production and metabolic flexibility. AMPK activation by PSMs improves lipid and glucose metabolism, reducing insulin resistance and enhancing fatty acid oxidation. For example, quercetin and epigallocatechin gallate (EGCG) promote AMPK-mediated suppression of acetyl-CoA carboxylase (ACC), enhancing fatty acid breakdown. PSMs also influence the AMPK pathway in concert with other signaling networks. For example, resveratrol activates sirtuin 1 (SIRT1), which synergizes with AMPK to enhance mitochondrial biogenesis and energy homeostasis [30]. Thus, PSMs modulate the AMPK pathway through direct and indirect mechanisms, promoting energy homeostasis, mitochondrial biogenesis, and metabolic health. These effects position PSMs as potential therapeutic agents for conditions such as obesity, diabetes, and age-related mitochondrial dysfunction.

Modulation of the Sirtuin Pathway by PSMs

PSMs modulate the sirtuin pathway, a critical regulator of cellular metabolism, stress resistance, and aging. Sirtuins are a family of NAD⁺ dependent deacetylases and ADP-ribosyl transferases that influence mitochondrial biogenesis, energy metabolism, and cellular survival [31]. By activating sirtuins, PSMs enhance mitochondrial function and protect against metabolic and age-related diseases. Resveratrol, quercetin, and curcumin are well-known activators of SIRT1, the most studied member of the sirtuin family. Resveratrol directly interacts with SIRT1, enhancing its deacetylase activity. SIRT1 activation deacetylates key transcriptional regulators like peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), promoting mitochondrial biogenesis, improving oxidative phosphorylation, and enhancing cellular energy efficiency [32, 33]. PSMs indirectly enhance sirtuin activity by increasing intracellular NAD⁺ levels, a critical cofactor for sirtuin function. For instance, compounds like polyphenols and alkaloids can stimulate NAD⁺ biosynthesis by activating enzymes in the NAD⁺ salvage pathway, thereby sustaining sirtuin-mediated mitochondrial and metabolic regulation [32, 34].

SIRT3, a mitochondrial sirtuin, regulates the activity of enzymes involved in oxidative phosphorylation, fatty acid oxidation, and antioxidant defense [31]. Resveratrol and EGCG enhance SIRT3 activity, leading to deacetylation of proteins like superoxide dismutase 2 (SOD2) and ATP synthase, which reduces reactive oxygen species (ROS) production and supports mitochondrial energy metabolism [35, 36]. Curcumin and catechins modulate sirtuins to reduce oxidative stress and inflammation. SIRT1 activation by these metabolites upregulates antioxidant enzymes and suppresses pro-inflammatory signaling pathways, protecting mitochondrial and cellular integrity under stress conditions [32, 37]. Many PSMs activate sirtuins in synergy with AMPK, another key metabolic regulator [32]. This crosstalk amplifies the beneficial effects on mitochondrial biogenesis, energy metabolism, and stress resistance.

PSMs modulate the sirtuin pathway by directly activating sirtuins, enhancing NAD⁺ availability, and promoting mitochondrial health. These effects highlight the therapeutic potential of PSMs in combating metabolic dysfunction, aging, and oxidative stress-related diseases.

PSMs target Nrf2 Pathway

Plant secondary metabolites (PSMs) modulate the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, a key regulator of cellular defense mechanisms against oxidative stress and inflammation [38]. The Nrf2 pathway controls the expression of genes encoding antioxidant enzymes, detoxification proteins, and other cytoprotective molecules, making it crucial for maintaining mitochondrial and cellular

health. Curcumin, resveratrol, and sulforaphane, activate Nrf2 by disrupting its interaction with Kelch-like ECH-associated protein 1 (Keap1) [39, 40, 41]. Under normal conditions, Keap1 binds Nrf2 and targets it for degradation. PSMs induce oxidative or electrophilic modifications in Keap1, releasing Nrf2 to translocate into the nucleus and initiate gene transcription. Activated Nrf2 enhances the expression of antioxidant enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), and heme oxygenase-1 (HO-1). Catechins and quercetin have been shown to boost these defenses, reducing reactive oxygen species (ROS) levels and protecting mitochondria from oxidative damage [42, 43]. PSMs modulate the Nrf2 pathway to promote mitochondrial health. Nrf2 activation improves mitochondrial function by reducing oxidative damage and supporting the expression of genes involved in mitochondrial quality control and biogenesis. For example, resveratrol enhances mitochondrial resilience through Nrf2-mediated antioxidant defenses [40]. Flavonoids and isothiocyanates stimulate Nrf2-dependent expression of phase II detoxification enzymes, such as glutathione-S-transferases (GSTs) and NAD(P)H quinone oxidoreductase 1 (NQO1) [44, 45]. These enzymes neutralize toxic intermediates, safeguarding mitochondrial integrity. By activating Nrf2, PSMs suppress pro-inflammatory signaling pathways, including NF-κB. This crosstalk reduces chronic inflammation, a driver of mitochondrial dysfunction and metabolic diseases. This pathway works alongside other protective mechanisms, such as AMPK and sirtuins, amplifying their impact on mitochondrial and cellular health. PSMs activate the Nrf2 pathway to enhance antioxidant defenses, support mitochondrial function, and reduce inflammation. These effects make PSMs valuable in preventing oxidative stress-related diseases and promoting metabolic and cellular resilience.

PSMs aid in maintenance of mitochondrial structure and function

The antioxidant effects of PSMs significantly modulate mitochondrial structure and function by mitigating oxidative stress and preserving mitochondrial integrity. These metabolites, including polyphenols, terpenoids, and alkaloids, act as potent scavengers of reactive oxygen species (ROS), which are critical regulators of mitochondrial dynamics, quality control, and bioenergetics [19, 20]. Mitochondria are a major site of ROS production, especially under stress. Excessive ROS can damage mitochondrial membranes, proteins, and DNA, leading to impaired structure and function. Polyphenols (e.g., flavonoids like quercetin and resveratrol), neutralize ROS, reducing oxidative damage to mitochondrial lipids, proteins, and mtDNA. Prevent mitochondrial membrane permeabilization, preserving mitochondrial integrity. Carotenoids (e.g., β-carotene), protect mitochondrial membranes by preventing lipid

peroxidation [46]. Antioxidant PSMs stabilize mitochondrial membrane potential, a key factor for ATP production and ion homeostasis. Flavonoids (e.g., catechins), prevent the collapse of $\Delta\Psi_m$ by reducing oxidative stress on membrane proteins and complexes of the electron transport chain (ETC). Phenolic acids (e.g., ferulic acid), strengthen mitochondrial membranes by reducing oxidative damage to cardiolipin, a lipid critical for ETC function [47].

ROS often suppress mitochondrial biogenesis by damaging signaling pathways involved in mitochondrial renewal. Antioxidant PSMs activate PGC-1 α (peroxisome proliferator-activated receptor-gamma coactivator 1-alpha), a key regulator of mitochondrial biogenesis, through indirect modulation of oxidative stress. Stimulate pathways such as AMPK and SIRT1, which are sensitive to the oxidative state and promote mitochondrial turnover and growth [47]. Antioxidant PSMs enhance mitochondrial efficiency by protecting the electron transport chain (ETC) from oxidative damage. They prevent inhibition of ETC complexes caused by ROS-induced modifications and reduce ROS-mediated uncoupling of oxidative phosphorylation, ensuring efficient ATP production [46]. Excessive ROS can trigger the opening of the mitochondrial permeability transition pore (mPTP), leading to swelling and cell death. Terpenoids (e.g., saponins) inhibit ROS-mediated mPTP opening, preventing mitochondrial swelling and apoptosis. Alkaloids (e.g., berberine) protect mitochondria by stabilizing the mPTP under oxidative stress conditions [48]. ROS are key signals for mitophagy (selective degradation of damaged mitochondria). Excessive ROS, however, can overwhelm the system, leading to mitochondrial dysfunction. Antioxidant PSMs normalize ROS levels, allowing proper activation of mitophagy pathways (e.g., PINK1/Parkin) and promote the selective removal of damaged mitochondria, maintaining a healthy mitochondrial population. Under abiotic and biotic stress, antioxidant PSMs help maintain mitochondrial structure and function by enhancing stress signaling pathways, such as those mediated by salicylic acid and jasmonic acid and support mitochondrial resilience to fluctuating ROS levels, ensuring energy supply during stress [49, 50]. The antioxidant effects of plant secondary metabolites preserve mitochondrial structure and function by reducing ROS levels, stabilizing mitochondrial membranes, maintaining $\Delta\Psi_m$, and supporting biogenesis and dynamics. These actions ensure mitochondrial health, energy production, and cellular adaptation to environmental stress. The ability of PSMs to fine-tune oxidative balance highlights their importance in organismal resilience and stress tolerance.

PSMs regulate mitochondrial dynamics

PSMs regulate mitochondrial dynamics by influencing the processes of mitochondrial fusion, fission, and their interplay

with quality control mechanisms. Mitochondrial dynamics is critical for maintaining mitochondrial function, ensuring cellular homeostasis, and responding to environmental stress (Figure 2). Mitochondrial Fusion involves merging mitochondrial membranes to maintain mitochondrial integrity, distribute mitochondrial DNA (mtDNA), and buffer against stress. Polyphenolic Compounds like resveratrol and quercetin promote mitochondrial fusion by enhancing the expression of fusion-related proteins such as MFN1/2 (Mitofusin 1 and 2) and OPA1 (Optic Atrophy 1) [51, 52]. Also, support oxidative balance, reducing damage to mitochondria, which facilitates effective fusion. Carotenoids, like β -carotene, stabilize mitochondrial membranes, indirectly favoring fusion over fission under normal or moderate stress conditions [46]. Mitochondrial Fission enables the segregation of damaged mitochondria for removal via mitophagy and contributes to mitochondrial biogenesis. Terpenoids and Phenolics increase activity of DRP1 (Dynamin-related protein 1), the primary mediator of mitochondrial fission and mitigate the excessive production of ROS, which triggers protective mitochondrial fission during stress [53]. Some alkaloids like nicotine or berberine influence mitochondrial fission to adapt to stress conditions by maintaining energy balance and ensuring rapid mitochondrial turnover [21, 54].

Certain PSMs regulate the dynamic equilibrium between fusion and fission, a critical factor for maintaining mitochondrial function. Flavonoids (e.g., catechins) help fine-tune the fusion-fission balance by modulating signaling pathways such as AMPK and mTOR, which indirectly affect mitochondrial dynamics [55]. Phenolic acids (e.g., gallic acid) protect mitochondria from oxidative stress, ensuring proper interplay between fusion and fission processes [56].

PSMs enhance mitochondrial membrane stability, which is vital for maintaining dynamics. Antioxidants like ascorbic acid (vitamin C, a metabolite derivative) preserve $\Delta\Psi_m$, indirectly supporting fusion and suppressing unnecessary fission [57]. Phenolics reduce lipid peroxidation in mitochondrial membranes, preventing structural disruptions. Mitochondrial fission often precedes mitophagy to isolate damaged parts of mitochondria. PSMs like curcumin and resveratrol activate mitophagy pathways (e.g., PINK1/Parkin), which are tightly linked to mitochondrial fission, ensuring that damaged mitochondria are removed efficiently [28, 29].

Under abiotic or biotic stress, PSMs act as ROS scavengers, limiting oxidative damage and favoring controlled mitochondrial dynamics. Thereby, Influence stress-responsive transcription factors that regulate genes associated with mitochondrial fusion and fission (e.g., through modulation of salicylic acid or jasmonic acid pathways) [49, 50]. Plant secondary metabolites regulate mitochondrial dynamics by maintaining the balance between fusion and fission, stabilizing mitochondrial membranes,

and influencing signaling pathways involved in stress responses and mitochondrial quality control. These actions optimize mitochondrial function, enabling plants to adapt to environmental challenges and maintain energy homeostasis. The STRING 12.0 database was used to build the protein-protein interaction network with all the genes targeted by PSM's and involved in maintenance of mitochondrial dynamics (Figure 2) [58]. The interaction value of "high confidence >0.7" was used for the analysis. The thickness of the network edges reflects the strength of the data. The proteins are listed in the Table 2 with their potential functions. The network indicates that PSM target proteins work in a concerted fashion to bring about the modulation in the mitochondrial structure and function. MAPK acts as a signaling protein in controlling the gene expression, cell division and stress responses.

Role of PSMs in mitophagy

PSMs play a crucial role in regulating mitophagy, a selective form of autophagy that eliminates damaged or dysfunctional mitochondria. Mitophagy is vital for cellular homeostasis, stress responses, and adaptation to environmental changes. PSMs such as phenolics, terpenoids, and alkaloids influence mitophagy through various mechanisms. Compounds like flavonoids, phenolic acids, and tannins modulate signaling pathways such as AMPK (AMP-activated protein kinase) and mTOR (mechanistic target of rapamycin) [30, 59]. Activation of AMPK promotes mitophagy by upregulating autophagy-related genes (ATGs) and enhancing mitochondrial quality control. Carotenoids and saponins, can reduce oxidative stress by stabilizing mitochondrial membranes, indirectly promoting mitophagy [46, 60].

Table 2: List of genes targeted by different PSMs and their potential function in maintenance of mitochondrial dynamics and function

GENE	NAME	FUNCTION
BAK1	BCL2 Antagonist/Killer 1	BAK1 is a pro-apoptotic protein that promotes mitochondrial outer membrane permeabilization, leading to the release of apoptogenic factors like cytochrome c and the activation of caspases, thereby inducing apoptosis
BAX	BCL2 Associated X	BAX is a pro-apoptotic protein that promotes cell death by increasing mitochondrial membrane permeability, leading to the release of cytochrome c and activation of caspases
BCL2	B-cell lymphoma 2	BCL2 is a protein that inhibits apoptosis, promoting cell survival by preventing the release of apoptogenic factors from the mitochondria
BCL2L1	Bcl-2-like protein 1	BCL2L1 is a protein that regulates apoptosis by acting as either an inhibitor or activator of cell death, depending on its isoform
BMS1	BMS1 Ribosome Biogenesis Factor	BMS1 is a protein that plays a crucial role in the assembly of the small ribosomal subunit by facilitating the processing and maturation of pre-ribosomal RNA
CAMKK2	Calcium/Calmodulin-Dependent Protein Kinase 2	CAMKK2 is an enzyme that regulates various physiological processes, including energy homeostasis, glucose metabolism, and neuronal signaling, by phosphorylating downstream kinases like CaMK1, CaMK4, and AMPK.
CASP3	Caspase 3	CASP3 is a crucial effector caspase that mediates the execution phase of apoptosis by cleaving various cellular proteins following activation by initiator caspases
CASP9	Caspase 9	CASP9 is an initiator caspase that plays a crucial role in apoptosis by activating downstream effector caspases, leading to programmed cell death
CYCS	Cytochrome c, somatic	CYCS is a small heme protein that plays a critical role in the mitochondrial electron transport chain and apoptosis by transferring electrons and triggering caspase activation
DENR	Density-Regulated Protein	DENR is involved in the regulation of translation reinitiation and ribosome recycling, playing a crucial role in protein synthesis
GABPA	GA Binding Protein Transcription Factor Subunit Alpha	GABPA is a transcription factor that regulates gene expression, mitochondrial function, and cellular differentiation by binding to specific DNA sequences
KEAP1	Kelch-like ECH-associated protein 1	KEAP1 is a regulatory protein that controls the activity of the transcription factor Nrf2, playing a crucial role in the cellular response to oxidative stress by promoting the degradation of Nrf2 under normal conditions
MAPK1	Mitogen-activated protein kinase 1 also Known as ERK2	MAPK1 (ERK2) is an enzyme that regulates cell proliferation, differentiation, transcription, and development by integrating multiple biochemical signals.

MAPK8	Mitogen-Activated Protein Kinase 8	MAPK8 also known as JNK1, is an enzyme that regulates cellular processes such as proliferation, differentiation, transcription, and apoptosis by integrating multiple biochemical signals
MFN1	Mitofusin 1	MFN1 is a mitochondrial outer membrane GTPase that mediates mitochondrial fusion, helping maintain mitochondrial network integrity and function
MFN2	Mitofusin 2	MFN2 is a mitochondrial membrane protein that regulates mitochondrial fusion, morphology, and function, and also plays a role in endoplasmic reticulum-mitochondrial tethering
MTOR	Mechanistic Target of Rapamycin	MTOR is a serine/threonine protein kinase that regulates cell growth, proliferation, motility, survival, protein synthesis, autophagy, and transcription by forming two distinct complexes, mTORC1 and mTORC2
NFKB1	Nuclear Factor Kappa B Subunit 1	NFKB1 is a transcription factor that regulates immune and inflammatory responses, cell growth, and apoptosis by controlling the expression of various genes
OPA1	Optic Atrophy 1	OPA1 is a mitochondrial dynamin-like GTPase that regulates mitochondrial fusion, cristae structure, and energy production, playing a crucial role in maintaining mitochondrial integrity and function
PINK1	PTEN-induced putative kinase 1	PINK1 is a mitochondrial serine/threonine-protein kinase that protects cells from stress-induced mitochondrial dysfunction by initiating mitophagy, the process of removing damaged mitochondria
PPARGC1A	Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha	PPARGC1A is a transcriptional coactivator that regulates genes involved in energy metabolism, mitochondrial biogenesis, and muscle fiber type determination
PRKAA1	Protein Kinase AMP-Activated Catalytic Subunit Alpha 1	PRKAA1 is a catalytic subunit of AMPK that acts as a cellular energy sensor, regulating metabolic pathways by phosphorylating key enzymes in response to changes in cellular energy status
SARM1	Sterile Alpha and TIR Motif Containing 1	SARM1 is an enzyme that acts as a sensor of metabolic stress and an executioner of neuronal cell body and axon death by hydrolyzing NAD ⁺
SIRT1	Sirtuin 1	SIRT1 is a NAD ⁺ -dependent deacetylase that regulates cellular stress responses, metabolism, and aging by deacetylating various transcription factors and proteins
SIRT3	Sirtuin 3	SIRT3 is a mitochondrial enzyme that regulates cellular metabolism, oxidative stress, and energy homeostasis by deacetylating and activating various mitochondrial proteins
SOD2	Superoxide Dismutase 2 (Mn)	SOD2 is a mitochondrial enzyme that protects cells from oxidative stress by converting superoxide radicals into hydrogen peroxide and oxygen
STK11	Serine/threonine-protein kinase 11	The STK11 gene, also known as LKB1, encodes a serine/threonine kinase that regulates cell polarity and functions as a tumor suppressor
TAOK2	TAO Kinase 2	TAOK2 is a serine/threonine-protein kinase that regulates various cellular processes, including stress response, apoptosis, and cytoskeletal organization, by activating the MAPK14/p38 MAPK signaling pathway

PSMs, especially those with strong antioxidant properties, reduce excessive reactive oxygen species (ROS) production. Since ROS act as a key signal for mitophagy, PSMs help fine-tune this response, preventing overactivation or suppression of mitophagy. For example, resveratrol (a stilbenoid) and curcumin (a polyphenol) directly lower oxidative stress and enhance mitochondrial turnover through PINK1/Parkin-mediated mitophagy [51, 29]. Some of the PSMs can regulate mitochondrial fusion and fission processes, which are prerequisites for mitophagy (Figure 2). They can enhance mitochondrial fission by modulating the expression or activity of proteins like DRP1 (dynamin-related protein 1). PSMs also interact with phytohormones such as jasmonic acid and salicylic acid, which are known to influence cellular autophagy [49, 50].

These signaling molecules may amplify mitophagy

under stress conditions like pathogen attack or abiotic stress. During biotic or abiotic stress, PSMs contribute to the removal of damaged mitochondria through stress-responsive pathways. For instance, alkaloids like nicotine can activate stress-response genes that are linked to mitochondrial quality control mechanisms [54]. PSMs may regulate mitophagy indirectly by mediating inter-organelle communication (e.g., signaling between mitochondria and the ER). This helps coordinate energy metabolism and stress adaptation. Plant secondary metabolites regulate mitophagy by modulating oxidative stress, mitochondrial dynamics, and autophagy-related signaling pathways. This regulatory role not only aids in maintaining mitochondrial health but also enhances cell or organism's resilience to environmental challenges. Understanding these mechanisms can provide insights into improving stress tolerance and metabolic efficiency in organisms.

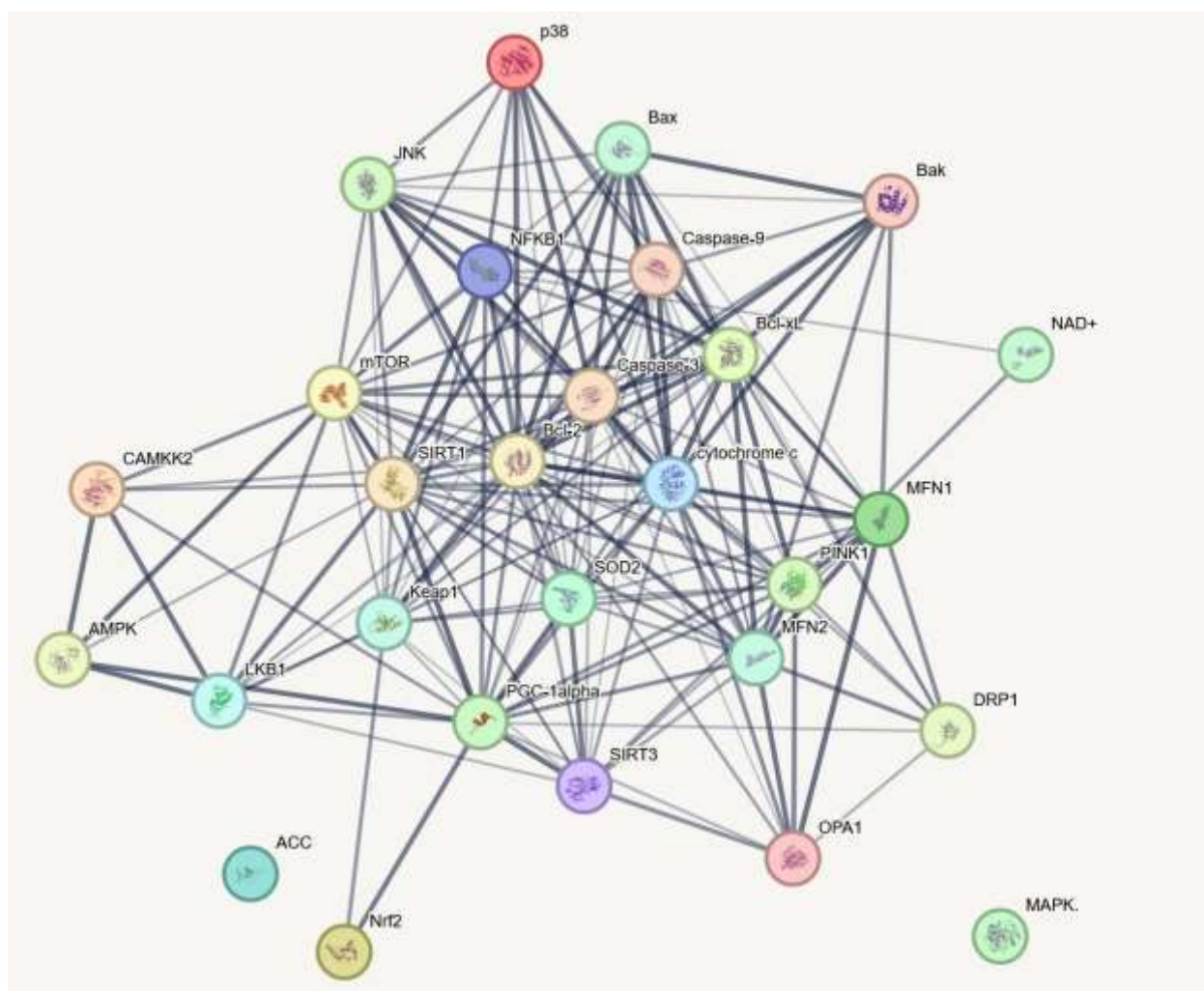


Figure 2: The PSM targeting protein-protein interaction network involved in maintenance of mitochondrial dynamics. The interaction value of “high confidence >0.7” was used and the thickness of the network edges reflects the strength of the data.

PSMs with apoptotic activity

PSMs play a significant role in modulating mitochondrial apoptotic pathways by targeting key molecular processes involved in mitochondrial membrane integrity, reactive oxygen species (ROS) production, and pro-apoptotic signaling. Apoptosis is a regulated form of cell death often mediated by mitochondria, particularly through the intrinsic (mitochondrial) pathway (Figure 3). The mitochondrial outer membrane permeability (MOMP) is a critical step in apoptosis, controlled by Bcl-2 family proteins (anti-apoptotic like Bcl-2/Bcl-xL and pro-apoptotic like Bax/Bak). Polyphenol compounds like resveratrol and quercetin can modulate the balance between anti-apoptotic and pro-apoptotic proteins by upregulate Bcl-2/Bcl-xL to stabilize mitochondrial membranes and prevent apoptosis [61, 62]. Down-regulate Bax/Bak to inhibit the release of cytochrome c. Terpenoids (e.g., carotenoids and saponins) and protect mitochondrial

membranes from stress-induced depolarization, reducing the likelihood of cytochrome c release [63, 64]. Cytochrome c release from mitochondria into the cytosol is a hallmark of apoptosis, as it activates the apoptosome and downstream caspases. Flavonoids reduce oxidative stress and stabilize mitochondrial membranes, directly inhibiting cytochrome c release [24].

Alkaloids (e.g., berberine) inhibit stress-induced mitochondrial swelling and permeability transition pore (mPTP) opening, preventing cytochrome c leakage [65]. Excessive ROS production from mitochondria can trigger apoptosis by damaging mitochondrial components and activating pro-apoptotic signaling. Antioxidant PSMs like Polyphenols (e.g., catechins, curcumin) scavenge ROS, preventing oxidative damage to mitochondrial DNA (mtDNA), proteins, and lipids [56]. Lower ROS levels to suppress activation of stress-responsive apoptotic pathways

(e.g., JNK and p38 MAPK). Phenolic acids (e.g., ferulic acid) maintain redox balance and protect mitochondrial function under stress [66]. Loss of $\Delta\Psi_m$ is an early event in mitochondrial apoptosis, leading to the activation of apoptotic pathways. Flavonoids and terpenoids stabilize $\Delta\Psi_m$ by inhibiting oxidative damage to membrane components. Supporting the activity of the electron transport chain (ETC) and reducing ETC-derived ROS [22, 24].

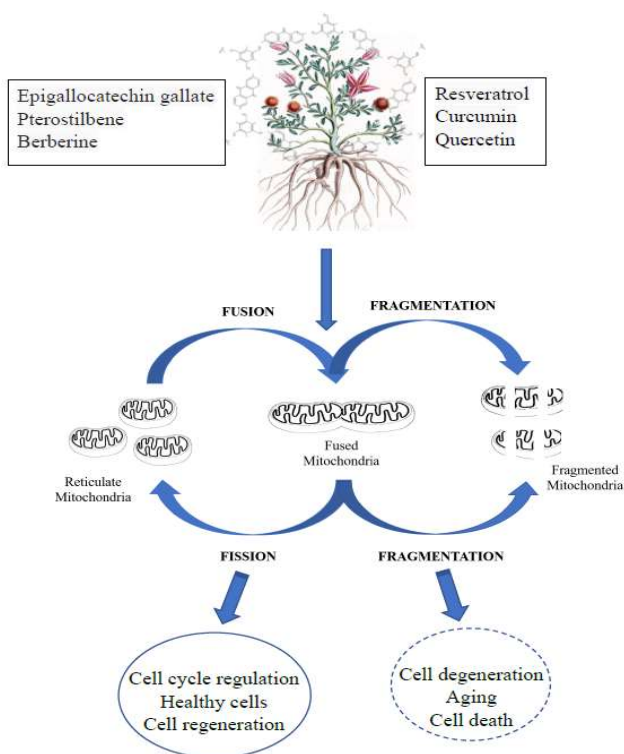


Figure 3: Role of PSMs in maintenance of mitochondrial dynamics and cell cycle.

PSMs modulate apoptotic signaling pathways by targeting key upstream regulators. Flavonoids activate the AMPK pathway, enhancing mitochondrial resilience and suppressing apoptosis [67]. Meanwhile, compounds like curcumin and resveratrol inhibit the pro-inflammatory NF- κ B pathway, reducing stress-induced apoptosis and promoting cellular survival under stress conditions [68]. Caspases are crucial enzymes in the process of apoptosis, with caspase-9 serving as an initiator activated upon apoptosome formation and caspase-3 acting as an executioner that cleaves cellular components to complete cell death. Polyphenols inhibit apoptosis by preventing the release of cytochrome c and the assembly of the apoptosome, thereby blocking the activation of caspase-9 and caspase-3 [56]. Similarly, alkaloids suppress caspase activity either directly or indirectly by modulating upstream factors such as reactive oxygen species (ROS) and Bcl-2 family proteins, ultimately interfering with the apoptotic pathway [65]. Under moderate stress,

certain PSMs precondition mitochondria by inducing mild, protective levels of reactive oxygen species (ROS), which enhance mitochondrial defense mechanisms. Phytohormones like salicylic acid and jasmonates regulate mitochondrial signaling, fine-tuning stress responses and delaying apoptosis under stress conditions [49, 50]. Additionally, isoprenoids support mitochondrial resilience by promoting biogenesis and repair, thereby reducing the likelihood of apoptotic signaling during prolonged stress. The mitochondrial permeability transition pore (mPTP) plays a critical role in regulating mitochondrial apoptosis. Plant secondary metabolites (PSMs) inhibit mPTP opening, preserving mitochondrial membrane potential ($\Delta\Psi_m$) and preventing the release of apoptogenic factors such as cytochrome c [20]. Compounds like curcumin and resveratrol stabilize the mPTP under oxidative stress, protecting mitochondria from apoptotic signaling.

PSMs exhibit dual roles in apoptosis depending on the context (Figure 3). In cancer cells, PSMs enhance apoptosis by selectively targeting dysfunctional mitochondria, inducing ROS-mediated cell death in tumor cells while sparing normal cells. Conversely, in stress-tolerant cells, such as plants under abiotic stress, PSMs prevent excessive apoptosis, promoting resilience and survival under adverse conditions. PSMs modulate mitochondrial apoptotic pathways by balancing oxidative stress, stabilizing mitochondrial membranes, and regulating pro- and anti-apoptotic proteins and signaling cascades. These effects contribute to the protective or pro-apoptotic roles of PSMs, depending on the physiological context, making them valuable in stress resilience, disease prevention, and therapeutic applications.

Constraints In Using Plant Secondary Metabolites As Mito-Nutraceuticals

Secondary metabolites in plants are not consistently present because their production is often influenced by environmental conditions, developmental stages, and stress factors [69]. These compounds are not essential for basic metabolic functions but play crucial roles in plant defense, pollinator attraction, and stress adaptation. For example, alkaloids may accumulate in response to herbivore attacks, while phenolics are produced under UV stress [70]. Additionally, secondary metabolite levels vary between species, tissues, and even individual plants within the same species [71, 72].

Plant secondary metabolites also interact with other foods in diverse ways, influencing their bioavailability, activity, and effects. These interactions involve enhancement of bioavailability, inhibition of nutrient absorption, synergistic effects, and co-metabolism, highlighting the complexity of their roles in a mixed diet [73, 74]. Certain compounds improve the absorption of secondary metabolites. For instance, flavonoids like quercetin are better absorbed when

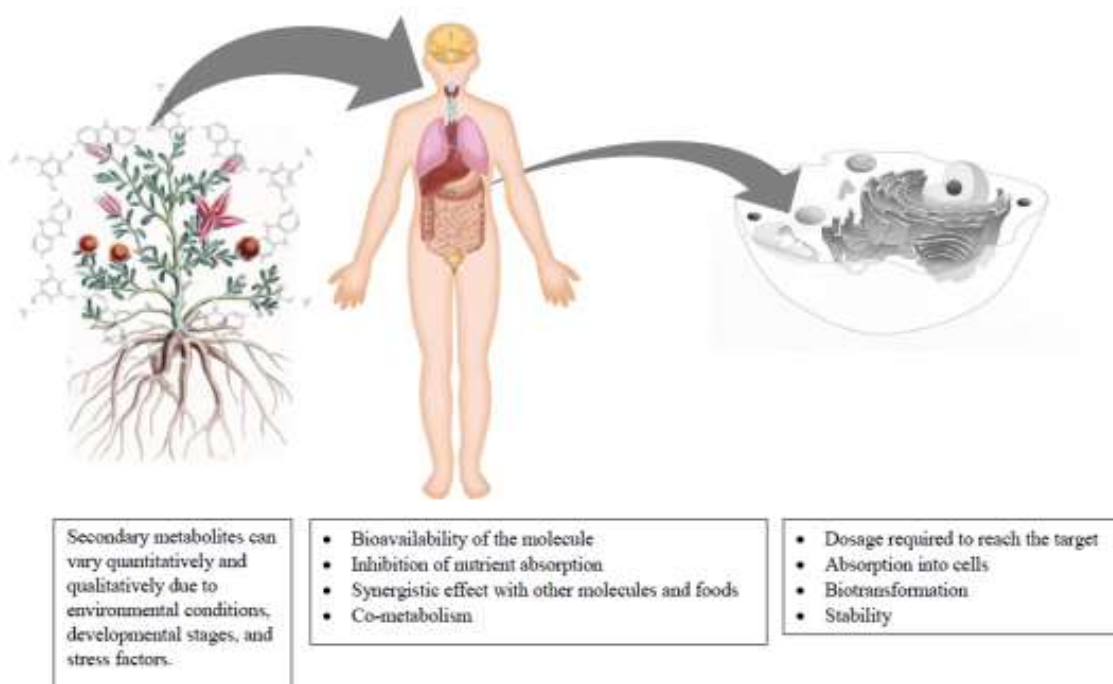


Figure 4: Constraints in exploiting PSMs as mito-nutraceuticals

consumed with fat-rich foods, as their solubility increases in the presence of lipids. Similarly, vitamin C enhances the stability and absorption of polyphenols, boosting their antioxidant properties [75]. Some secondary metabolites act as anti-nutrients by forming complexes with dietary proteins, carbohydrates, or minerals, reducing their bioavailability. Tannins bind to iron and proteins, lowering digestibility, while oxalates reduce calcium absorption, potentially leading to deficiencies or kidney stone formation [76]. Saponins interfere with fat absorption by forming complexes with lipids, and alkaloids can inhibit digestive enzymes, impairing nutrient utilization [77]. A comprehensive view of constraints in exploiting the PSMs as mito-nutraceuticals is summarized in Figure 4.

Secondary metabolites often work synergistically with other foods to enhance health benefits. For example, the combination of polyphenols from tea and anthocyanins from berries amplifies antioxidant activity [78]. Similarly, curcumin (from turmeric) and piperine (from black pepper) work together, with piperine enhancing curcumin's bioavailability and anti-inflammatory properties [79]. Dietary fiber from whole grains promotes the fermentation of plant polyphenols in the gut, boosting beneficial microbial metabolites. Secondary metabolites also interact with gut microbiota and enzymes during digestion, influencing their effects [80]. Polyphenols from tea or fruits are metabolized by gut microbes into bioactive compounds, which are enhanced by prebiotic-rich foods like fiber. Lipid co-metabolism occurs when fat-rich foods improve the solubility and absorption of fat-soluble metabolites like carotenoids. Conversely, tannins

and phytates may reduce nutrient availability by forming insoluble complexes, though foods like vitamin C-rich citrus can counteract these effects [81, 82]. While secondary metabolites may reduce nutrient bioavailability in some cases, they often exhibit significant health benefits, such as antioxidant, anti-inflammatory, and therapeutic properties. Their interactions with other foods underscore the importance of a novel methods for their targeted delivery to maximize their positive effects while minimizing potential drawbacks.

Future Directions

To overcome the constraints discussed above, one of the possible ways by which plant secondary metabolites can be exploited maximum for nutrient and nutraceutical activity is by developing plant secondary metabolite-loaded nanoparticles. Such formulation can offer several advantages, particularly in the fields of food science and medicine. They include:

- **Enhanced Bioavailability:** Many plant secondary metabolites, such as flavonoids, alkaloids, and terpenoids, have low water solubility and poor bioavailability. Nanoparticles improve their solubility, absorption, and uptake in biological systems, ensuring higher therapeutic efficiency [83].
- **Improved Stability:** Secondary metabolites are prone to degradation by environmental factors such as heat, light, and pH changes. Encapsulation within nanoparticles protects these compounds, maintaining their activity and prolonging shelf life [83].

- **Controlled Release:** Nanoparticles allow for sustained or controlled release of secondary metabolites, ensuring prolonged therapeutic or biological effects. This reduces the need for frequent dosing, improving and patient compliance [84].
- **Targeted Delivery:** Nanoparticles can be engineered to deliver plant metabolites to specific cells, tissues, or organs, minimizing off-target effects and maximizing efficacy. It protects the molecules from enzymatic and microbial bio-transformations in the digestive system and enables them to be delivered intact. This is particularly beneficial for cancer therapy, where targeted delivery can reduce toxicity to healthy cells [84].
- **Multifunctionality:** Nanoparticles can carry multiple secondary metabolites or combine them with other therapeutic agents, creating synergistic effects. For example, co-delivery of antioxidants and anti-inflammatory agents enhances overall efficacy [85].
- **Reduced Toxicity:** By targeting specific sites and controlling release, nanoparticles minimize the systemic exposure of secondary metabolites, reducing potential side effects or toxicity [85].
- **Versatile Applications:** Plant secondary metabolite-loaded nanoparticles have diverse applications.
- **Biocompatibility and Sustainability:** Plant-derived metabolites are natural and generally biocompatible, and the use of nanoparticles can be aligned with eco-friendly approaches, reducing reliance on synthetic chemicals.
- **Overcoming Drug Resistance:** In medicine, nanoparticles can enhance the effectiveness of plant metabolites against drug-resistant pathogens or cancer cells by improving intracellular delivery and bioactivity [86].

Plant secondary metabolite-loaded nanoparticles combine the therapeutic potential of natural compounds with the advanced delivery capabilities of nanotechnology, offering a promising approach for food and nutraceutical applications. In summary, plant secondary metabolites modulate mitochondrial structure and function through pathways that enhance energy production, promote biogenesis, regulate antioxidant defenses, and maintain mitochondrial quality control. These molecular mechanisms position PSMs as potential therapeutic agents for improving mitochondrial health and combating diseases linked to mitochondrial dysfunction. Improving methods for targeted delivery can revolutionize mitochondrial therapeutics and can greatly impact human health.

Funding: Authors acknowledge fund support from the National Science Foundation HBCU-UP RIA Program (Award #2400398)

Institutional Review Board Statement: NA

Informed Consent Statement: NA

Data Availability Statement: NA

Acknowledgements

Authors wish to thank Dr. John Williams, Chair, Department of Natural Sciences, Albany State University for providing required infrastructure to carry out this research.

Conflict of Interest: The authors declare no conflicts of interest.

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