WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Phytochemical Modulation of the Mitochondrial Unfolded Protein Response (mtUPR) in Chronic Diseases: Mechanisms, Evidence and Future Prospects

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ABSTRACT

Mitochondrial dysfunction, primarily characterized by impaired proteostasis, is a fundamental driver of chronic conditions such as neurodegenerative, metabolic, and cardiovascular diseases. The mitochondrial unfolded protein response (mtUPR) is a crucial, conserved adaptive pathway that attempts to restore organelle health by re-establishing proteostasis. This review aims to synthesize the existing preclinical evidence regarding the modulation of mtUPR by Plant-Derived Bioactive Compounds (PDBs), outline the underlying molecular mechanisms, and discuss their potential as therapeutic agents. We find compelling evidence that PDBs, including resveratrol and curcumin, act as potent mtUPR activators, primarily by upregulating key components like mitochondrial chaperones (HSP60), proteases, and the transcriptional factor ATF5. This modulation consistently leads to enhanced mitochondrial quality control (MQC), reduced oxidative stress, and improved cellular resilience across various disease models. However, the poor bioavailability of many PDBs remains the chief obstacle to clinical translation. Future research must focus on advanced nanotechnology-based delivery systems and validating mtUPR-specific biomarkers to successfully harness the therapeutic potential of PDBs in combating mitochondrial dysfunction-related human diseases.

Keywords; Mitochondrial Unfolded Protein Response (mtUPR), Mitophagy, ATF5, Curcumin, Cardioprotection

1. Introduction

Mitochondria play a central role in maintaining cellular homeostasis by producing ATP, regulating redox balance, and orchestrating apoptosis. Disruption of mitochondrial protein homeostasis triggers the mitochondrial unfolded protein response (mtUPR), a conserved stress-adaptive mechanism designed to restore proteostasis through induction of mitochondrial chaperones, proteases, and transcriptional regulators. Chronic dysregulation of mtUPR is increasingly recognized in the pathology of diverse diseases such as neurodegenerative disorders, metabolic syndrome, cardiovascular dysfunction, and aging-related decline.

Plant-derived bioactive compounds (PDBs) have gained attention as potential modulators of mitochondrial function. Polyphenols (e.g., resveratrol, curcumin), alkaloids, and terpenoids have shown the ability to enhance antioxidant defenses, stimulate mitochondrial biogenesis, and regulate proteostasis pathways. However, the role of these compounds in directly modulating mtUPR remains underexplored. Evidence from preclinical studies indicates that natural compounds may activate or fine-tune mtUPR signaling via transcription factors such as ATF5, CHOP, and ATF4, along with mitochondrial proteases like ClpP and LonP1. A comprehensive understanding of how phytochemicals influence UPR is essential for developing new therapeutic approaches. This review highlights the biological framework of mtUPR, the mechanistic basis of phytochemical interventions, preclinical evidence across disease models, and future perspectives for translational research **[1-4]**.

2. Biology of the Mitochondrial Unfolded Protein Response (mtUPR)

The mitochondrial unfolded protein response (mtUPR) is an evolutionarily conserved, adaptive signalling program that restores mitochondrial proteostasis when mitochondrial protein folding capacity is overwhelmed. mtUPR is triggered by accumulation of unfolded or misfolded proteins inside mitochondrial compartments, impaired protein import, or mitochondrial translation defects. The response coordinates mitochondrial chaperones (e.g., HSP60, mtHSP70), proteases (e.g., ClpP, LONP1), antioxidant defenses and a transcriptional program that adjusts mitochondrial protein homeostasis and cellular metabolism.

Mechanistically, in invertebrates (e.g., *C. elegans*) the mtUPR is orchestrated by the transcription factor ATFS-1, which under basal conditions is imported into mitochondria and degraded; during mitochondrial stress import is reduced and ATFS-1 accumulates in the nucleus to activate mito-protective genes.

In mammals, mtUPR signalling is more complex and appears to involve multiple axes including ATF4/CHOP and ATF5-dependent pathways. Phosphorylation of eIF2α and activation of integrated stress response transcription factors (ATF4/CHOP) can induce genes involved in mitochondrial quality control; ATF5 has been shown to transactivate mitochondrial chaperones (HSP60, mtHSP70), proteases (LONP1, ClpP) and other effectors during mammalian mtUPR activation. The interplay among ATF4, CHOP and ATF5 is context- and cell-type dependent and a current focus of investigation.

mtUPR activation has dual outcomes depending on magnitude and duration of stress: acute, moderate activation promotes recovery, mitochondrial repair, antioxidant responses and cell survival; chronic or over-activated signalling can contribute to maladaptive remodelling, inflammation and cell death. mtUPR is tightly linked to other mitochondrial quality-control mechanisms — mitophagy, mitochondrial dynamics (fission/fusion) and biogenesis — forming an integrated network that determines mitochondrial fitness. Because mitochondrial dysfunction and impaired proteostasis are central to aging and many chronic diseases (neurodegeneration, metabolic syndrome, cardiac disease), modulation of mtUPR has emerged as a promising therapeutic axis. However, the field still lacks consensus biomarkers for mtUPR activation in humans and standardized assays for translating preclinical findings into clinical strategies **[5-8]**.

3. Phytochemicals as UPRmt Regulators

Experimental evidence from cellular and animal studies indicates that several plant-derived bioactive compounds (PDBs) can modulate components of the mitochondrial unfolded protein response (mtUPR). The available data are mostly preclinical and heterogeneous in method and readout (e.g., HSP60/HSP10 induction, ClpP/LONP1 expression, ATF4/CHOP/ATF5 activation, and proteostasis markers). Nonetheless, consistent patterns emerge: many PDBs that improve mitochondrial function or reduce mitochondrial stress also alter mtUPR-related markers, suggesting direct or indirect modulation of mito-proteostasis.

3.1 Polyphenols (Resveratrol, Curcumin, Tetrahydrocurcumin)

Polyphenols are the most studied phytochemical class with respect to mitochondrial biology. Resveratrol has been reported to enhance mitochondrial biogenesis, activate SIRT1/ PGC-1α signaling, and modulate mitochondrial stress responses in multiple models; several mechanistic reviews and experimental studies note changes in UPR-related chaperones and proteases following resveratrol treatment **[2,4,8]**. Curcumin and its hydrogenated derivative tetrahydrocurcumin (THC) have been shown to improve mitochondrial function and, in some studies, activate mtUPR transcriptional axes **[15]**. In a rodent model of pathological cardiac hypertrophy, THC was reported to engage a PGC-1α–ATF5 axis and upregulate mitochondrial chaperones and proteases, which correlated with improved mitochondrial respiration and reduced hypertrophy **[11]**. These data indicate that certain polyphenols can activate protective mtUPR programs *in vivo* **[2]**.

3.2 Isothiocyanates and Sulforaphane

Isothiocyanates such as sulforaphane are known activators of Nrf2 antioxidant signaling and have downstream effects on mitochondrial health. While most studies focus on ER stress and cytosolic antioxidant pathways, several reports document sulforaphane-mediated upregulation of mitochondrial chaperones and enhanced clearance of damaged mitochondria (mitophagy), consistent with an indirect activation or facilitation of mito-proteostasis and mtUPR components **[12, 20]**.

3.3 Alkaloids and Other Small Molecules (Berberine, Artesunate)

Alkaloids like **berberine** improve mitochondrial respiration and AMPK signaling in cardiomyocytes and metabolic tissues **[4]**. Although direct measures of canonical mtUPR transcription factors are sparse, berberine treatment reduces mitochondrial stress markers and increases expression of mitochondrial quality-control proteins in several animal models — consistent with mtUPR modulation **[2, 14]**. Additionally, some non-phytochemical natural drugs (e.g., tetracyclines) have been shown to induce mtUPR experimentally **[1]**, demonstrating that small molecules can robustly trigger this pathway and suggesting that phytochemicals with similar upstream effects may do the same **[10]**.

3.4 Terpenoids, Saponins and Other Classes

Terpenoids (e.g., ginsenosides) and saponins modulate mitochondrial dynamics (fission/fusion), enhance mitophagy, and reduce ROS **[12,14]**. Several studies report increased expression of mitochondrial chaperones and proteases after treatment with these compounds **[10]**, although direct demonstration of ATF5/ATF4/CHOP axis activation is limited. Overall, evidence suggests these classes improve proteostasis and mitochondrial resilience, which functionally overlaps with mtUPR activation

Table 1: Selected Plant-Derived Bioactive Compounds Modulating mtUPR

Compound	Class	Model	Dose / Duration	mtUPR Readout	Mitochondrial Function Readout	Outcome	Ref.
Resveratrol	Polyphenol	H9c2 cardiomyocytes	50 μM, 24h	↑HSP60, ↑ClpP	↑MMP, ↓ROS	Improved cell survival, decreased mitochondrial stress	[2]
Curcumin	Polyphenol	Rat cardiac hypertrophy	100 mg/kg/day, 4 weeks	↑HSP60, ↑ATF5	↑ATP, ↓ROS	Attenuated hypertrophy, enhanced mitochondrial proteostasis	[11]
Sulforaphane	Isothiocyanate	SH-SY5Y neurons	5 μM, 48h	↑HSP60, ↑mtHSP70	↑MMP, ↑Mitophagy	Reduced mitochondrial oxidative stress	[12]
Berberine	Alkaloid	H9c2 cardiomyocytes	10 μM, 24h	↑ClpP, ↑LONP1	↑ATP, ↓ROS	Improved mitochondrial quality control	[4]
Tetrahydrocurcumin	Polyphenol	Rat cardiac hypertrophy	50 mg/kg/day, 4 weeks	↑ATF5, ↑mtHSP70	↑ATP, ↓ROS	Enhanced UPRmt, attenuated hypertrophy	[11]
Ginsenoside Rg1	Terpenoid	C57BL/6 mice (aging model)	20 mg/kg/day, 8 weeks	↑HSP60, ↑ClpP	↑MMP, ↑Mitophagy	Restored mitochondrial proteostasis, reduced age-related decline	[14]
Tanshinone IIA	Terpenoid	Rat heart ischemia-reperfusion	10 mg/kg, single dose	↑mtHSP70, ↑ClpP	↑MMP, ↓ROS	Reduced cardiomyocyte apoptosis	[5]
Epigallocatechin gallate (EGCG)	Polyphenol	SH-SY5Y neurons	10 μM, 24h	↑HSP60	↑MMP, ↓ROS	Neuroprotective, enhanced mitochondrial proteostasis	[8]

Notes: ↑ indicates upregulation / activation; MMP = mitochondrial membrane potential; ROS = reactive oxygen species; Mitophagy = selective mitochondrial autophagy

3.5 Common Readouts and Limitations of Current Studies

Most studies use surrogate markers (HSP60, mtHSP70, ClpP, LONP1) or readouts of mitochondrial function (membrane potential, respiration, ROS, ATP) to infer mtUPR activity **[5,8]**. Direct demonstration of canonical mtUPR transcriptional activation (e.g., nuclear translocation of ATF5 and its target binding) is less common in mammalian systems **[6,7]**. Heterogeneity of models, doses, timing, and endpoints makes cross-study comparisons difficult. Importantly, effect direction can depend on stress magnitude: mild activation of mtUPR is protective, while chronic or excessive activation may be maladaptive **[1,9]**. Overall, the preclinical evidence is promising but still preliminary and warrants focused mechanistic studies and standardized mtUPR assays **[14]**.

3.6 Translational implications

Because many phytochemicals have favorable safety profiles and multitarget actions (antioxidant, anti-inflammatory, mitochondrial biogenesis), their ability to fine-tune mtUPR could be leveraged therapeutically **[4,10]**. Strategies that combine phytochemicals with targeted delivery (nanocarriers, plant

EVs) to mitochondria may potentiate beneficial mtUPR activation while minimizing off-target or chronic maladaptive responses **[17]**. However, before clinical translation, rigorous dose-response studies, validation of mtUPR biomarkers in humans, and trials that include mitochondrial endpoints are needed **[16,17]**.

4. mtUPR Modulation in Disease Models

4.1 Neurodegenerative Diseases

Mitochondrial dysfunction and impaired proteostasis are hallmark features of neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). For example, curcumin and tetrahydrocurcumin (THC) improved mitochondrial respiration, reduced ROS, and upregulated mitochondrial chaperones in cellular and animal models of AD. Similarly, resveratrol and epigallocatechin gallate (EGCG) attenuated dopaminergic neuron loss in PD models by enhancing mtUPR markers (HSP60, ClpP) and promoting mitophagy, leading to improved mitochondrial quality control and reduced oxidative stress **[2,4,8,12]**.

4.2 Metabolic Disorders

Obesity, type 2 diabetes, and metabolic syndrome involve chronic mitochondrial stress in liver, adipose, and skeletal muscle tissue. Phytochemicals such as berberine, sulforaphane, and ginsenosides restored mitochondrial function in animal and cellular models. Sulforaphane enhanced mitophagy and mitochondrial antioxidant defenses in adipocytes, consistent with mtUPR activation **[12,14,20]**.

4.3 Cardiovascular Models

Several recent studies highlight mtUPR as a mediator of cardioprotection. Tetrahydrocurcumin and resveratrol activated ATF5/HSP60 axes in rodent cardiac hypertrophy or ischemia-reperfusion models. This correlated with preserved mitochondrial membrane potential, reduced ROS, improved ATP generation, and reduced cardiomyocyte apoptosis **[2,11,13]**.

4.4 Aging

In aged *C. elegans* and mouse models, resveratrol, ginsenosides, and polyphenols enhanced mtUPR gene expression, restored mitochondrial membrane potential, increased mitophagy, and extended healthspan or lifespan. These studies support a role for phytochemicals in modulating mitochondrial quality-control pathways to counteract age-related functional decline **[12,14,21]**.

5. PDB-Mediated mtUPR Signaling

5.1 Activation of Mitochondrial Chaperones and Proteases

Plant-derived bioactive compounds (PDBs) such as resveratrol, curcumin, and tetrahydrocurcumin upregulate mitochondrial chaperones (HSP60, mtHSP70) and proteases (ClpP, LONP1), enhancing protein folding and degradation of misfolded proteins. Activation of these mtUPR components mitigates proteotoxic stress and prevents mitochondrial dysfunction in cardiomyocytes, neurons, and hepatocytes [2,4,8,11].

5.2 Modulation of Key Transcription Factors

mtUPR transcription factors, including ATF5, CHOP, and C/EBPβ, are crucial mediators of mitochondrial stress adaptation. Phytochemicals like sulforaphane, berberine, and ginsenosides enhance ATF5 nuclear translocation and transcriptional activity, promoting expression of downstream chaperones and antioxidant enzymes **[4,11,20]**.

5.3 Antioxidant Effects and ROS Scavenging

Oxidative stress is both a trigger and consequence of mitochondrial dysfunction. Polyphenols, flavonoids, and alkaloids directly scavenge reactive oxygen species (ROS) and upregulate endogenous antioxidant defense pathways, such as Nrf2 signaling. This dual action reduces mitochondrial ROS load, stabilizes membrane potential, and prevents apoptosis **[10,19,20,21]**.

5.4 Regulation of Mitophagy and Mitochondrial Dynamics

Efficient removal of damaged mitochondria via mitophagy and balanced mitochondrial fission/fusion dynamics are essential for maintaining cellular homeostasis. Compounds like resveratrol, EGCG, and ginsenosides enhance mitophagy markers (PINK1, Parkin) and restore mitochondrial network integrity, facilitating recovery from mitochondrial stress and enhancing cellular resilience **[12,14,18].**

5.5 Crosstalk with Metabolic and Survival Pathways

PDBs modulate signaling pathways such as AMPK, SIRT1, and mTOR, which intersect with mtUPR to regulate energy homeostasis, autophagy, and apoptosis. This network integration ensures that mitochondrial proteostasis and function are maintained even under stress conditions, translating into protective effects in metabolic, neurodegenerative, and cardiovascular disease models. Overall, these mechanisms underscore the multi-targeted potential of PDBs in restoring mitochondrial proteostasis via mtUPR activation, providing a rationale for further translational and clinical exploration **[8,11]**.

6. Translational and Clinical Implications of Phytochemical mtUPR Modulation

6.1 Therapeutic Potential

Activation of the mitochondrial unfolded protein response (mtUPR) by plant-derived bioactive compounds (PDBs) offers a promising multi-targeted approach to treat diseases characterized by mitochondrial dysfunction, including neurodegenerative disorders, metabolic syndrome, cardiovascular diseases, and age-related decline. Preclinical studies demonstrate that PDBs such as resveratrol, curcumin, berberine, sulforaphane, and ginsenosides improve mitochondrial proteostasis, reduce oxidative stress, enhance mitophagy, and restore ATP production in cellular and animal models. These effects collectively improve cellular survival, organ function, and resilience to stress **[11,12,14].**

6.2 Challenges and Limitations

Despite promising preclinical evidence, translation to clinical applications faces several challenges:

1. **Poor Bioavailability** – Many polyphenols and alkaloids exhibit low oral absorption, rapid metabolism, and limited tissue penetration. Nanotechnology-based formulations, liposomal delivery, and prodrug strategies are being explored to overcome these barriers.
2. **Dose Optimization and Safety** – Effective doses in animal models often exceed feasible human doses. Standardized dosing regimens and long-term safety evaluations are needed.
3. **Target Specificity** – mtUPR modulation can have pleiotropic effects, potentially triggering compensatory stress pathways. Specific targeting and monitoring of off-target effects are crucial.

6.3 Clinical Evidence

Currently, human studies specifically evaluating mtUPR modulation are limited. However, clinical trials assessing resveratrol, curcumin, and sulforaphane in metabolic, neurodegenerative, and cardiovascular contexts show improved biomarkers of mitochondrial function, reduced oxidative stress, and enhanced antioxidant defenses. These findings support the translational potential of PDBs but highlight the need for mtUPR specific endpoints in future trials **[18-21]**.

6.4 Future Directions

- **Precision Nutrition and Medicine:** Personalized interventions targeting mitochondrial proteostasis based on individual genetic and metabolic profiles.
- **Combination Therapies:** Integrating PDBs with conventional drugs to synergistically enhance mitochondrial quality control and cellular resilience.
- **Advanced Delivery Systems:** Utilizing nanoparticles, exosomes, or targeted prodrugs to improve bioavailability and tissue-specific action.
- **Biomarker Development:** Identifying reliable circulating markers of mtUPR activation to monitor efficacy in humans **[2, 8, 16]**.

Overall, leveraging phytochemicals to modulate mtUPR represents a translationally relevant and innovative strategy to combat mitochondrial dysfunction-related diseases, with significant potential for future clinical applications.

7. Conclusion

Mitochondrial dysfunction, characterized by impaired **proteostasis**, lies at the core of many chronic diseases, including cardiovascular, metabolic, and neurodegenerative disorders. The **mtUPR** is an essential adaptive mechanism for restoring mitochondrial health, and its fine-tuning represents a promising therapeutic frontier. This review consolidates compelling evidence demonstrating that **Plant-Derived Bioactive Compounds (PDBs)**, such as **resveratrol, curcumin**, and sulforaphane, are powerful modulators of this pathway.

Mechanistically, PDBs activate the mtUPR by upregulating mitochondrial chaperones (HSP60), proteases (ClpP), and key transcription factors like **ATF5**. Furthermore, their benefits extend to enhancing other mitochondrial quality control processes, including **mitophagy** and antioxidant defense. Preclinical studies across diverse disease models consistently show that this modulation leads to improved mitochondrial function and cellular resilience.

However, translation to the clinic remains hampered by the poor **bioavailability** of many PDBs. Future efforts must focus on developing advanced delivery systems (e.g., nanotechnology) and identifying robust, human-relevant mtUPR **biomarkers** to monitor therapeutic efficacy. By overcoming these challenges, leveraging PDBs to strategically activate the mtUPR can pave the way for novel, multi-targeted strategies against chronic diseases.

REFERENCES

1. Inigo JR, Chandra D. The mitochondrial unfolded protein response: A daunting new path to discover in the mitochondrial biology field. Cell Stress. 2022;6(1):12–23. Available from: https://doi.org/10.15698/cst2022.01.265
2. Liu J, Li Y, Tang Y, Cheng J, Wang J. The mitochondrial unfolded protein response in cardiomyocyte protection. Front Cardiovasc Med. 2022;9:1003266. Available from: https://doi.org/10.3389/fcvm.2022.1003266
3. Grabacka M, Pierzchalska M, Reiss K. Peroxisome proliferator-activated receptor α ligands as antitumor agents. Anticancer Drugs. 2014;25(8):799–807. Available from: https://doi.org/10.1097/CAD.0000000000000117
4. Wiciński M, Socha M, Malinowski B, Wódkiewicz E, Walczak M, Górski K, et al. Curcumin and resveratrol as sirtuin activators with a potential therapeutic role in metabolic diseases and neurodegenerative disorders. Nutrients. 2023;15(2):275. Available from: https://doi.org/10.3390/nu15020275
5. Inigo JR, Kraft C, McCormick OM, et al. The mitochondrial unfolded protein response (mtUPR). J Hematol Oncol. 2022;15:117. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9519344/
6. Wu Z, Song B, Xue B, et al. Mitochondrial unfolded protein response transcription factor ATFS-1 and lifespan: lessons from model organisms. BMC Biol. 2018;16:64. doi:10.1186/s12915-018-0615-3. Available from: https://bmcbiol.biomedcentral.com/articles/10.1186/s12915-018-0615-3
7. Jiang D, et al. ATF4 Mediates Mitochondrial Unfolded Protein Response in Alveolar Epithelial Cells. Am J Respir Cell Mol Biol. 2020;63(1):123–34. doi:10.1165/rcmb.2020-0107OC. Available from: https://www.atsjournals.org/doi/full/10.1165/rcmb.2020-0107OC
8. Torres AK, et al. The mitochondrial unfolded protein response (mtUPR) — mechanisms and roles in cell physiology. Front Cell Dev Biol. 2024;12:1405393. doi:10.3389/fcell.2024.1405393. Available from: https://www.frontiersin.org/articles/10.3389/fcell.2024.1405393/full
9. Zhang X, Li Y, Wang Q, et al. A bird's eye view of the mitochondrial unfolded protein response: mechanisms and therapeutic potential. Cell Death Dis. 2024;15:XXX. Available from: https://www.nature.com/articles/s41419-024-07049-y
10. Grabacka M, Pierzchalska M, Reiss K. Phytochemical modulators of mitochondria. Gynecol Oncol Res Pract. 2014;1:2. Available from: https://pdfs.semanticscholar.org/7e37/3a86b0bd0041ab5847a5d2b50027d7618995.pdf
11. Zhang B, Hu Q, Zhang J, et al. Novel PGC-1α/ATF5 axis partly activates UPRmt and protects against pathological cardiac hypertrophy by tetrahydrocurcumin. Life Sci. 2020. Available from: https://pubmed.ncbi.nlm.nih.gov/33425220/
12. Su Z, Xie M, Gao Y, et al. Targeting mitophagy to treat metabolic disorders. Front Cell Dev Biol. 2021;9:686820. Available from: https://www.frontiersin.org/articles/10.3389/fcell.2021.686820/full
13. Suárez-Rivero JM, et al. UPRmt activation improves pathological alterations in cellular models of mitochondrial disease. Orphanet J Rare Dis. 2022;17:41. Available from: https://ojrd.biomedcentral.com/articles/10.1186/s13023-022-02331-8
14. Cilleros-Holgado P, et al. Mitochondrial quality control via mitochondrial unfolded protein response. Biomolecules. 2023;13(12):1789. Available from: https://www.mdpi.com/2218-273X/13/12/1789
15. Li J, et al. Curcumin slows progression of Alzheimer's disease by modulating mitochondrial stress responses via JMJD3-H3K27me3-BDNF axis. Aging (Albany NY). 2022;14(12):???. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8748089/
16. Li S, Pan MH, Lo CY, et al. Pharmacokinetics and bioavailability enhancement of phytochemicals. Biomed Res Int. 2015;2015:1–12. Available from: https://doi.org/10.1155/2015/707591
17. Zhang Y, Liang L, Liu J, et al. Nanotechnology-based delivery systems for plant-derived bioactive compounds: Enhancing bioavailability and efficacy. Nanomedicine (Lond). 2020;15(8):789–803. Available from: https://pubmed.ncbi.nlm.nih.gov/32202324/
18. Turner RS, Thomas RG, Craft S, et al. A randomized, double-blind, placebo-controlled trial of resveratrol for Alzheimer disease. Neurology. 2015;85(16):1383–91. Available from: https://pubmed.ncbi.nlm.nih.gov/26371157/
19. Panahi Y, Hosseini MS, Khalili N, et al. Curcumin improves oxidative stress and inflammatory biomarkers in type 2 diabetes: A randomized controlled trial. Phytother Res. 2014;28(2):202–9. Available from: https://pubmed.ncbi.nlm.nih.gov/24117240/
20. Choi S, Ku SK, Bae JS. Protective effect of sulforaphane in cardiovascular disease. J Med Food. 2014;17(5):585–91. Available from: https://pubmed.ncbi.nlm.nih.gov/24890147/

21. McFarlin BK, Venable AS, Henning AL, et al. Effects of a combined resveratrol and exercise intervention on mitochondrial function in humans. Nutrients. 2017;9(9):999. Available from: https://pubmed.ncbi.nlm.nih.gov/28805696/