UNLOCKING THE THERAPEUTIC POTENTIAL OF RESVERATROL

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Abstract: Resveratrol (3,4′,5-trihydroxy-trans-stilbene), a stilbene-class polyphenolic molecule, arises as a secondary metabolite in more than 70 plant species in response to environmental stresses. Its discovery traces back to 1939 when Takaoka isolated it from *Veratrum grandiflorum O*. Resveratrol synthesis in plants follows the phenylpropanoid pathway triggered by factors like UV radiation and microbial attack. Grapes, peanuts, soybeans, berries, and Japanese knotweed stand out as primary sources, with dark grape extracts and giant knotweed being particularly rich reservoirs. Extraction techniques encompass supercritical fluid, subcritical water, solid-phase, pressurized liquid, ultrasound-assisted, and microwave-assisted methods. Despite rapid absorption in the small intestine and hepatic metabolism through glucuronidation and sulfation, resveratrol's bioavailability remains constrained due to limited solubility, instability, and swift metabolism. To overcome this, strategies such as nanoformulation, nanoparticle delivery, solid dispersions, and lipid-based formulations are explored to enhance oral bioavailability. Resveratrol known for its diverse health benefits spanning cardiovascular protection, cancer prevention, anti-aging properties, blood sugar stabilization, and anti-inflammatory effects, resveratrol is poised for significant market growth, supported by a range of available supplements. While generally safe, high doses may lead to gastrointestinal discomfort. Overall, resveratrol emerges as a promising therapeutic agent for managing various ailments and promoting overall well-being.

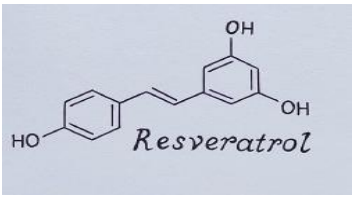
Key words: Resveratrol, Metabolism, Molecular mechanism, Therapeutic potential, Safety, Tolerability

History

Takaoka first discovered resveratrol, also known as 3,4,5-trihydroxy-trans-stilbene, in 1939 from *Veratrum grandiflorum O*. Later, in 1963, it was isolated from the roots of Japanese knotweed. Notably, in 2004, Harvard University professor David Sinclair played a pivotal role in co-founding Sirtris Pharmaceuticals and developing a resveratrol formulation.

Introduction

Resveratrol, classified as a secondary metabolite, falls into the category of polyphenolic compounds known as stilbenes. It is synthesized in over 70 plant species as a response to various environmental stressors such as mechanical damage, microbial infections, and exposure to UV radiation. Chemically, Resveratrol is referred to as 5-[(E)-2-(4-hydroxyphenyl) ethenyl] benzene-1,3-diol according to IUPAC nomenclature. Its molecular structure involves two phenol rings connected by a methylene double bond, resulting in 3,5,4-trihydroxystilbene. Resveratrol naturally occurs in two isomeric forms, trans-resveratrol, and cis-resveratrol. While both isomers exhibit biological activity, trans-resveratrol, being the more stable form, predominantly contributes to the various biological functions associated with resveratrol.



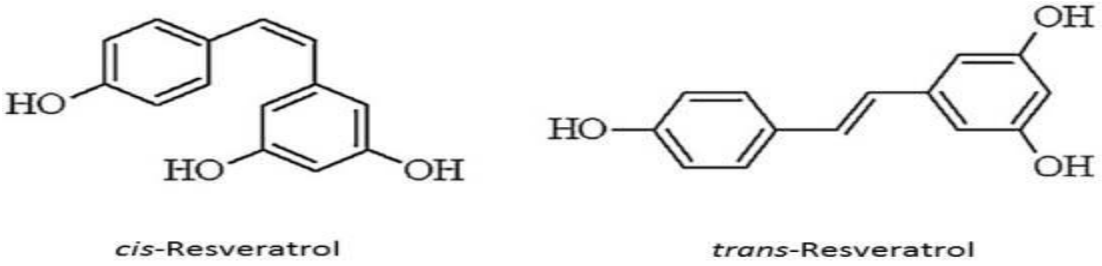
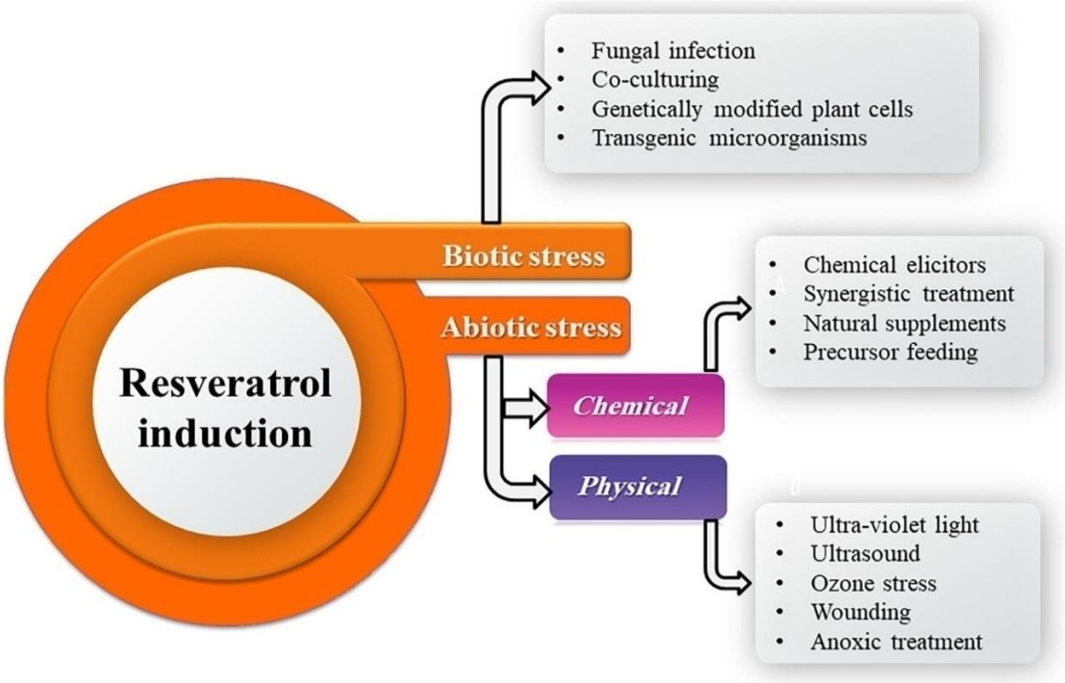


Figure 1: Chemical structure of Resveratrol

Resveratrol Induction



Resveratrol production can be enhanced through both biotic and abiotic stresses. Under biological induction, factors such as fungal infection and co-culturing have been obseResveratroled to significantly influence resveratrol biosynthesis, leading to a notable increase in accumulation by up to 40%. However, resveratrol synthesis is time-consuming and yields relatively low amounts, often being season-specific. Thus, mimicking the biosynthetic pathway in genetically modified plants and microorganisms holds promise as an approach to address these limitations.

In terms of biotic stresses, resveratrol production can be augmented by stimulating chemical, physical, and biological elicitors. Physical induction, for instance, UV radiation (350 nm, 20 min) has been shown to promote resveratrol biosynthesis significantly. Similarly, ultrasound (40 kHz, 10 min) treatment enhances metabolite biosynthesis by improving cell permeability.

Chemical induction methods involve the use of various substances such as amino acid precursors like phenylalanine and tyrosine, which have been found to stimulate resveratrol production effectively. Additionally, chemical elicitors like salicylic acid and cyclodextrin, along with precursor feeding using compounds like p-coumaric acid and cinnamic acid, contribute positively to resveratrol biosynthesis.

The combined use of multiple elicitors has shown synergistic effects, ozone treatment, wounding and anoxic treatment leads to more efficient enhancement of secondary product

biosynthesis from microbial or plant sources.

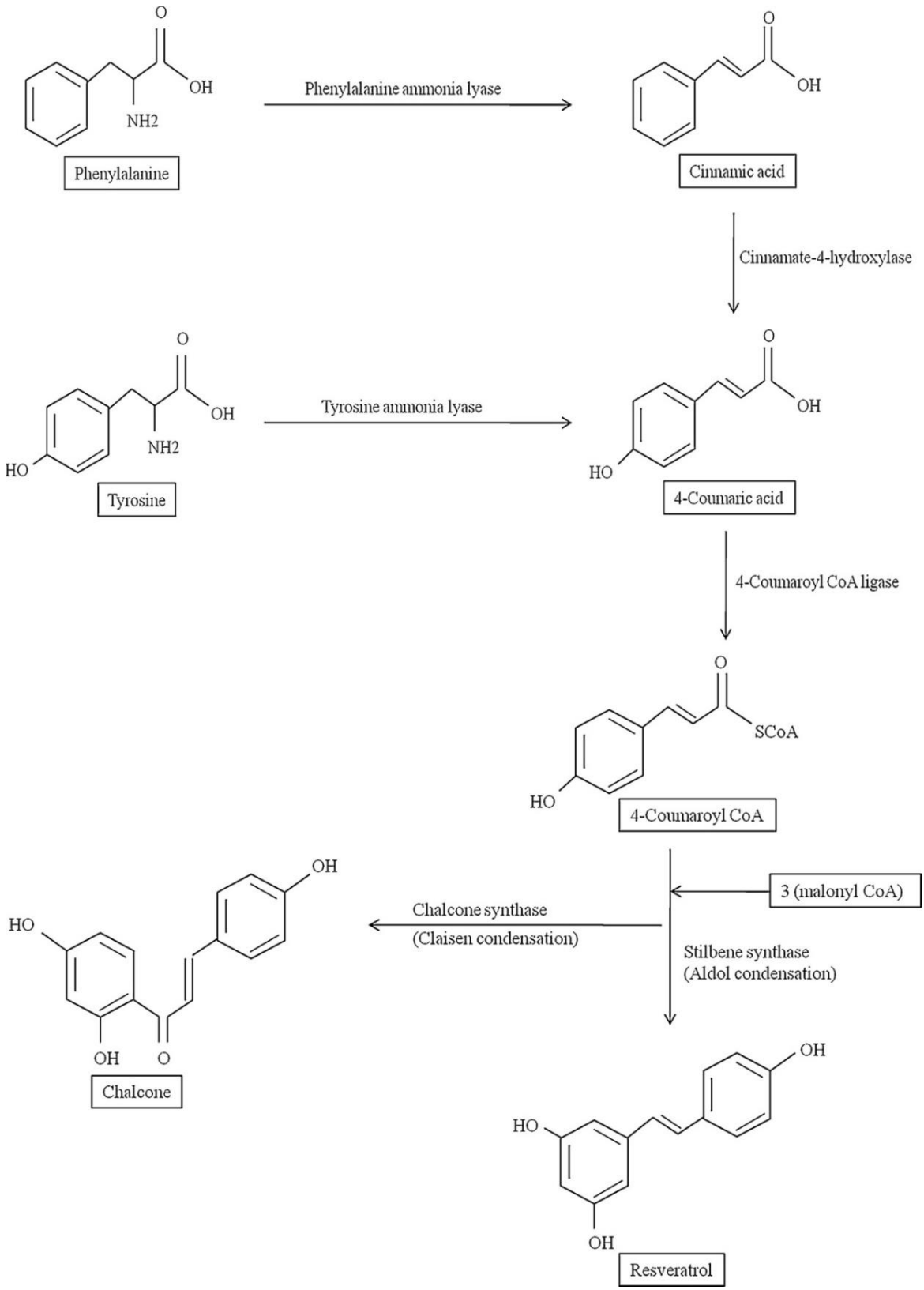
Physical properties of resveratrol

Chemical formula	$C_{14}H_{12}O_3$
Molecular weight	228.25 g/mol
Boiling point	253 -255℃
Appearance	White powder with a faint yellow tint
Solubility	Water (0.03 g/L), Ethanol (50 g/L) and Dimethyl sulfoxide (16 g/L)
Other names	3,5,4'-trihydroxy-cis-stilbene Trans-resveratrol 3,5,4'-trihydroxy-trans-stilbene 3,4,5-stilbenetriol (E)-5-(p-hydroxystyryl) resorcinol Trans-3,5,4-trihydrozystilbene

Resveratrol has a chemical formula of C14H12O3 and a molecular weight of 228.25 g/mol. The substance is observed in the form of a white powder, with a faint yellow hue. The boiling point of the substance falls within the range of 253 to 255°C. Regarding solubility, it has limited solubility in water (0.03 g/L), considerable solubility in ethanol (50 g/L), and solubility in dimethyl sulfoxide (16 g/L). Resveratrol is also known as 3,4,5-stilbenetriol, trans-3,5,4-trihydrozystilbene, 3,5,4'-trihydroxy-cis-stilbene, (E)-5-(p-hydroxystyryl) resorcinol, and 3,5,4'-trihydroxy-trans-stilbene.

Bio-synthesis of Resveratrol

Resveratrol is synthesised in plants through the phenylpropanoid pathway as a secondary metabolite in reaction to environmental factors such UV light, microbial infection, and fungicides. The manufacturing method employs aromatic amino acids L-phenylalanine and L-tyrosine. L-Phenylalanine ammonia lyase and L-tyrosine ammonia lyase accelerate the deamination process of these amino acids, resulting in the production of cinnamic acid and 4-coumaric acid, respectively. Cinnamic acid is subjected to hydroxylation, which is catalysed by cinnamate-4-hydroxylase, resulting in the conversion of cinnamic acid to 4-coumaric acid. The enzyme 4-coumaroyl CoA ligase catalyses the conversion of 4 coumaric acid to 4-coumaroyl-CoA, which is an active intermediate. Resveratrol is formed by the condensation of 4-coumaroyl-CoA with malonyl-CoA, which is then followed by cyclization. This process is catalysed by stilbene synthase.


Phenylalanine
Phenylalanine ammonia lyase
Cinnamic acid
Cinnamate-4-hydroxylase
Tyrosine
Tyrosine ammonia lyase
4-Coumaric acid
4-Coumaroyl CoA ligase
4-Coumaroyl CoA
3 (malonyl CoA)
Chalcone synthase
(Claisen condensation)
Stilbene synthase
(Aldol condensation)
Chalcone
Resveratrol

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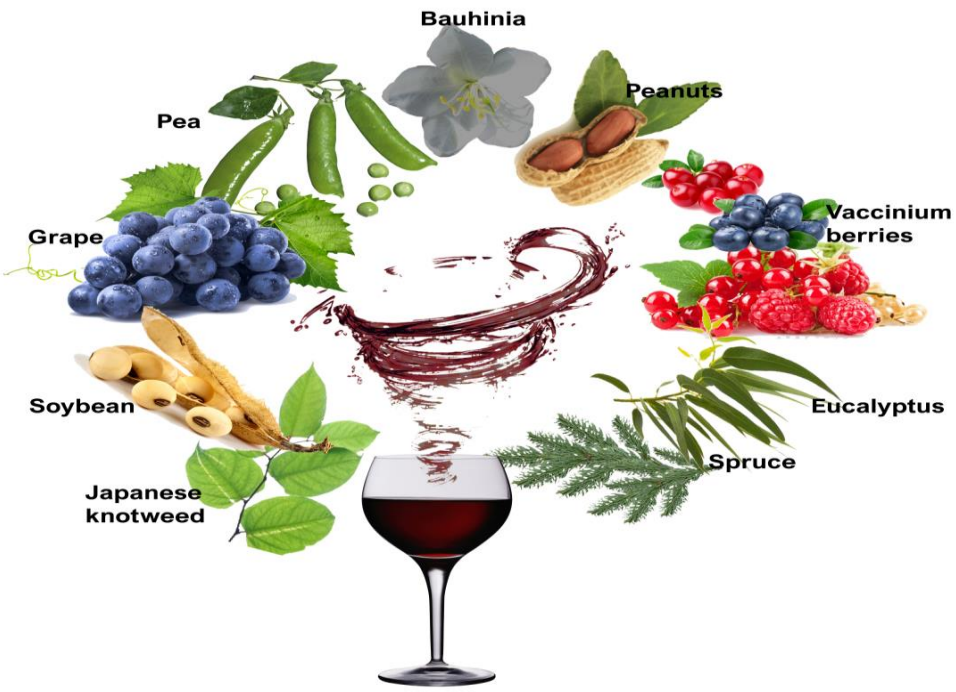
Sources/Occurance



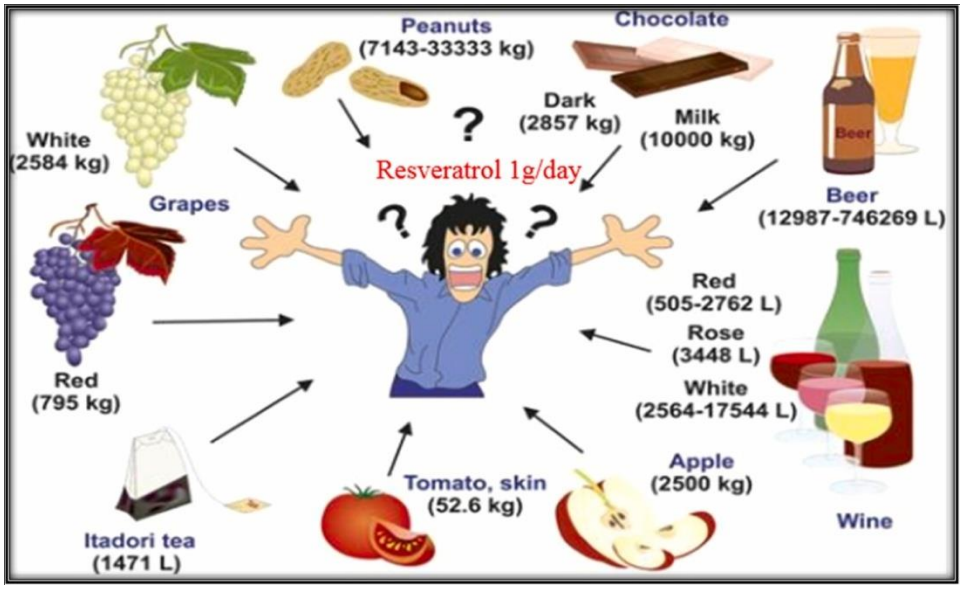
Major sources include grapes (*V. vinifera*) and grape products (must, wine), soybean (*Glycine max*), peanuts (*Arachis hypogaea*), berries (*Vaccinium* spp.), pea (*Pisum sativum*), spruce (*Picea excelsa*), Japanese Knotweed (*Fallopia japonica*), eucalyptus (*Eucalyptus sp.*) and bauhinia (*Bauhinia racemosa*).

Below is a catalog of sources containing resveratrol along with their respective concentrations

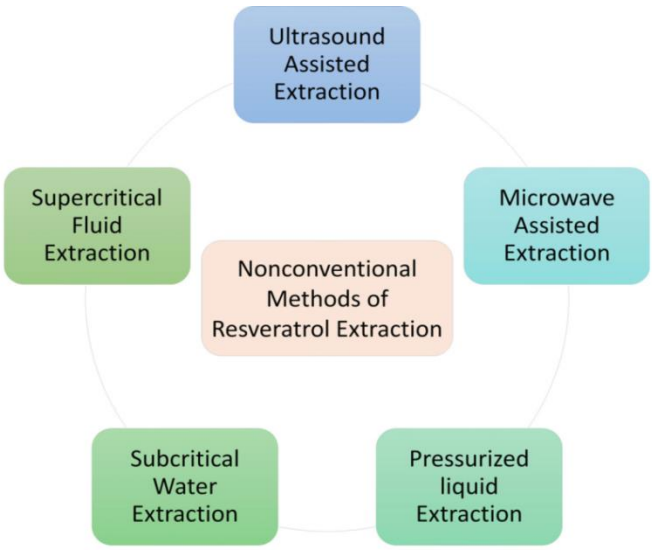
Sources	Resveratrol
Wine	0.32-15.35 µg/g
Peanut butter	0.02-0.98 µg/g
Peanuts	0.01-0.07 µg/g
Green peanuts	0.19-0.72 µg/g
Polygonum cuspidatum	296-377 µg/g
Green grapes	0.02-0.32 µg/g
Black grapes	0.95-1.88 µg/g
Raisins	0.0005-0.003 µg/g
Grape juice-black	Traces-0.09 µg/g
Grape juice-green	Traces-0.01 µg/g
White wines (Spanish)	0.05-1.80 mg/l
Rosé wines (Spanish)	0.43-3.52 mg/l
Red wines (Spanish)	1.92-12.59 mg/l
Red wines (global)	1.98-7.13mg/l
Red grape juice (Spanish)	1.14-8.69 mg/l

Particularly profuse natural reservoirs of resveratrol are dark grape compounds derived from Vitis vinifera and penetrating giant knotweed (*Polygonum cuspidatum*). Labrusca and muscadine grapes contain an abundance of resveratrol as well. In addition to blueberries, mulberries, strawberries, hops, peanuts and other food items, its presence is detected in a variety of other plants, including lilies, spruce, and Eucalyptus.

The quantity of beverages and foods required to reach a therapeutic dose will differ. If an individual's aim to consume 1 gram of resveratrol daily, the amount of food and drink consumed is illustrated in the figure below.



Extraction methods of resveratrol



Extraction of resveratrol typically involves the following methods:

Supercritical Fluid Extraction: In this method, supercritical carbon dioxide is used as a solvent to extract resveratrol from plant material.

Subcritical water extraction: Water can be used as a solution between 100 and 374 °C and under enough pressure to stay liquid.

Solid-Phase Extraction (SPE): SPE involves passing a solution containing resveratrol through a solid material that selectively adsorbs the compound. The resveratrol is then eluted from the solid phase using a suitable solvent, yielding a purified extract.

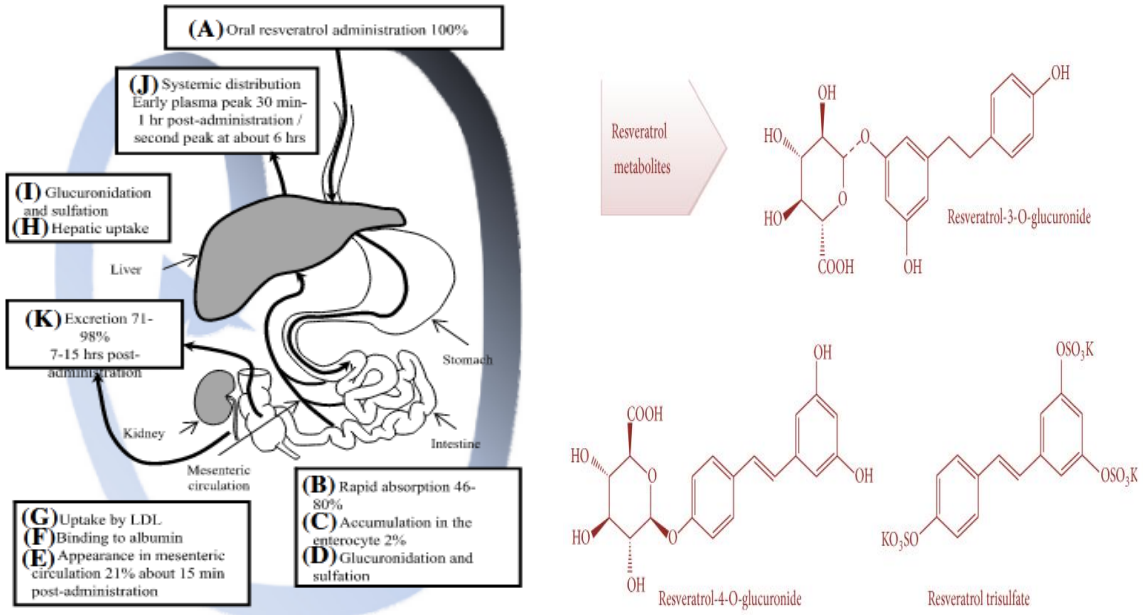
Pressurized liquid extraction (PLE): PLE, also known as accelerated solvent extraction (ASE), is a technique used for extraction that operates at high temperature and pressure.

Ultrasound-Assisted Extraction: Ultrasound waves are used to disrupt cell walls and enhance the release of resveratrol from plant material into the solvent.

Microwave-Assisted Extraction: Microwave-assisted extraction uses microwave radiation to heat the solvent and accelerate the extraction process.

These methods can be optimized based on factors such as the type of plant material, desired purity of the extract, and efficiency of extraction. Additionally, combination methods or novel techniques may be developed to improve extraction yields and reduce processing times further.

Absorption Metabolism and Bioavailability



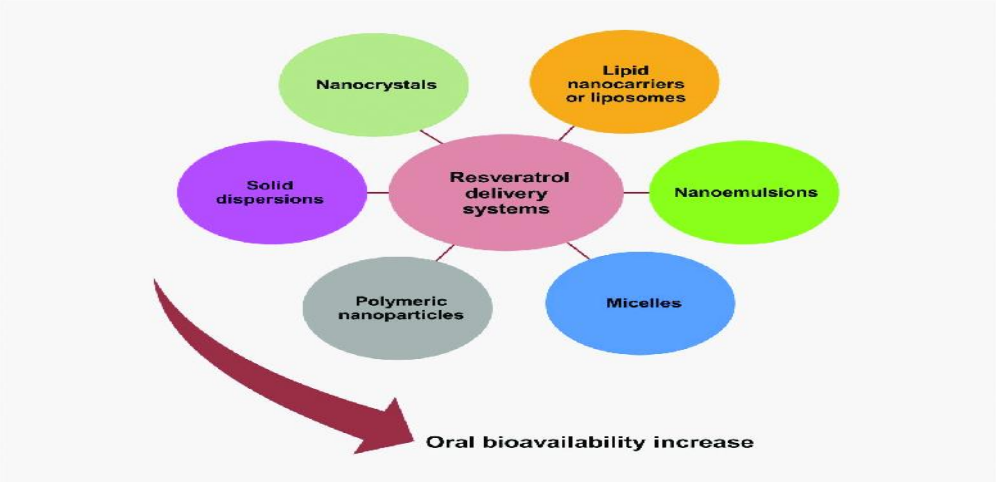
Resveratrol, derived from either food or supplements, undergoes fast absorption (46-80%) in the small intestine. Within the gut, it experiences glucuronidation and sulfation processes facilitated by glucuronosyltransferases and sulfotransferases. The metabolites of resveratrol are taken up by active transport and attach to albumin and lipoproteins in the circulation. These complexes function as reservoirs for resveratrol, enabling its dissemination to cells by dissociating when they encounter cells with albumin and lipoprotein receptors.

Resveratrol is transported to the liver through the hepatic portal system, where it undergoes phase II metabolism, generating glucuronide and sulfate forms with the help of glucuronosyltransferases and sulfotransferases. After ingestion, resveratrol is detectable in the blood after 30 minutes, peaks after 60 minutes, and remains detectable for up to 6 hours, with a surge attributed to enteric recirculation of metabolites. Excretion occurs mainly through urine or feces, with 71-90% excreted within 7-15 hours post-administration.

Factors affecting Bioavailability of Resveratrol

The bioavailability of resveratrol is low, less than 1%, primarily due to its poor water solubility (0.05 mg/L), chemical instability, and susceptibility to oxidation and light sensitivity. It undergoes rapid metabolism in the liver and quick excretion, resulting in a short biological half-life of 8 to 14 minutes. Factors such as pH and temperature also affect its bioavailability.

Approaches to improve resveratrol Oral Bioavailability



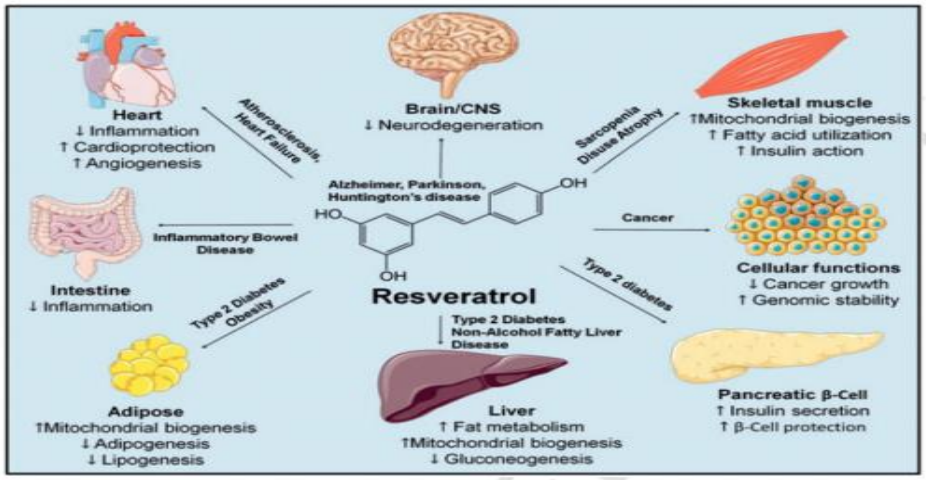
Enhancing the oral bioavailability of resveratrol is crucial for maximizing its therapeutic efficacy. Various effective strategies include nanoformulation, nanoparticle delivery, nanoemulsions, solid dispersions, micelles, and nanocrystals.

One approach involves encapsulating resveratrol within nanoparticles such as liposomes or polymeric nanoparticles. This encapsulation shields the compound from degradation and enhances its solubility and absorption in the gastrointestinal tract. By reducing the particle size, these formulations improve the solubility and stability of resveratrol, thereby increasing its surface area for absorption.

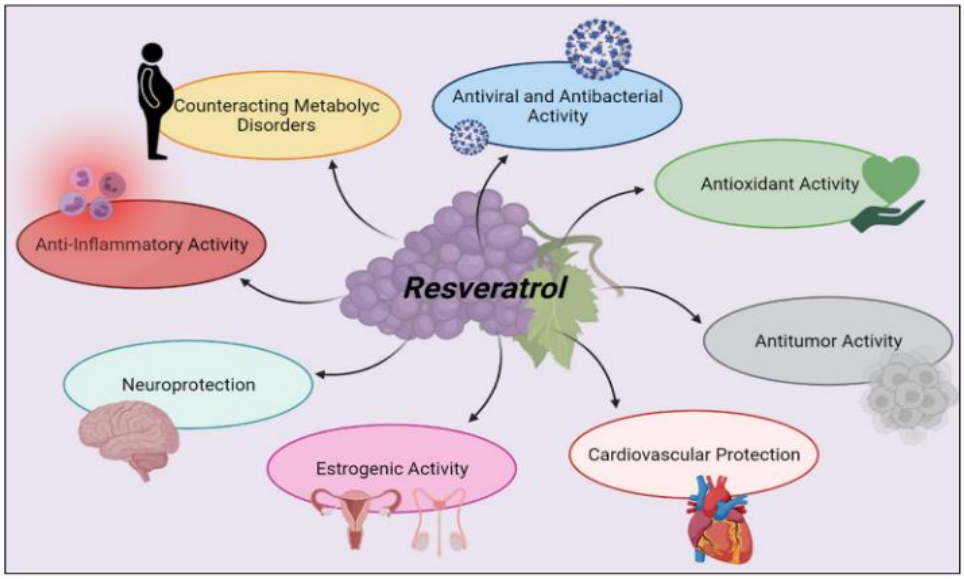
Another method is dispersing resveratrol within a polymeric matrix to boost its solubility and dissolution rate, thereby enhancing absorption. Utilizing Solid Lipid Nanoparticles can also safeguard resveratrol from degradation and improve absorption through enhanced lipid solubility.

Furthermore, co-administering resveratrol with Lipid-Based Formulations or alongside fatty meals can enhance its absorption due to its lipophilic nature, consequently improving its oral bioavailability.

Beneficial effects of resveratrol on different organs

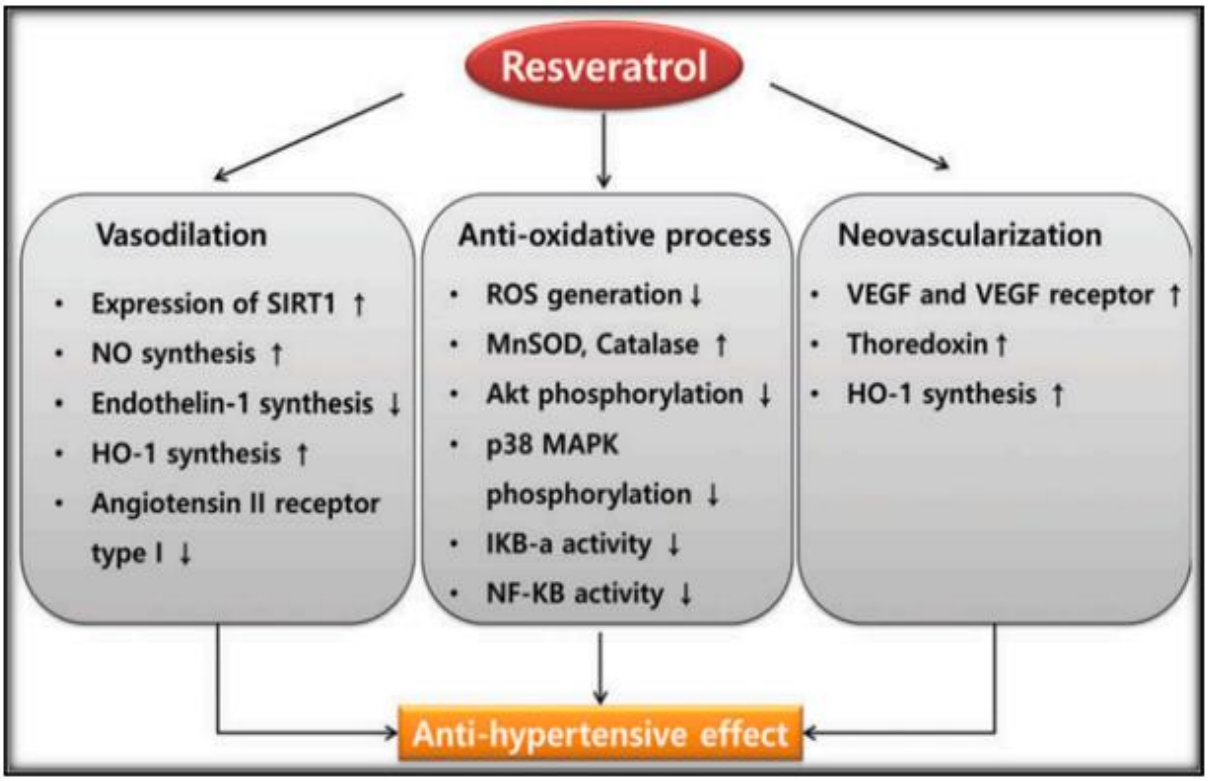


Biological properties



Resveratrol offers a broad spectrum of health advantages including cardiovascular protection, cancer prevention, anti-aging effects, enhanced energy production, blood sugar stabilization, and anti-inflammatory properties, ultimately contributing to overall wellness and disease prevention. Its mechanisms of action involve influencing gene expression, enhancing mitochondrial function, activating the immune system, and regulating various biochemical pathways.

Antihypertensive effects of Resveratrol

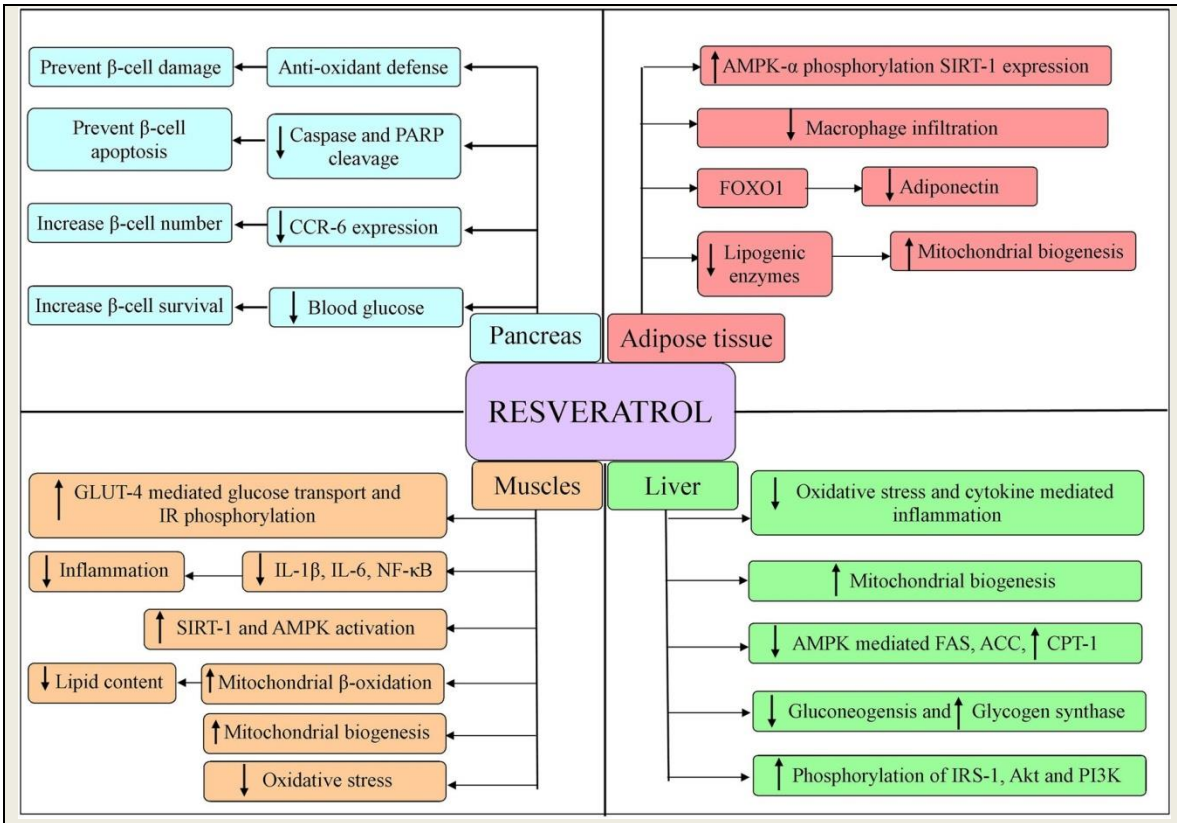


Resveratrol exhibits its blood pressure-lowering effects through various mechanisms, including vasodilation, antioxidative actions, and neovascularization. It primarily targets SIRT1 and sirtuins, leading to vasodilation by upregulating endothelial nitric oxide production. Additionally, it promotes the production of heme oxygenase-1 (HO-1), which is a precursor to bilirubin, resulting in a blood pressure-lowering action.

Furthermore, resveratrol decreases the levels of angiotensin II receptors and inhibits the production of endothelin, both of which are substances that cause blood vessels to constrict. The antioxidative effects of this substance include inhibiting the creation of reactive oxygen species (ROS), phosphorylation of Akt, and the activity of IKB, p38 MAPK, and NF-KB. At the same time, it increases the levels of manganese superoxide dismutase (MnSOD) and catalase.

Resveratrol also regulates redox processes and keeps cells in homeostasis by boosting thioredoxin synthesis and raising the expression of vascular endothelial growth factor (VEFG) and its receptors, both of which contribute to neovascularization. Furthermore, it promotes the production of HO-1, a compound with anti-inflammatory properties.

Antidiabetic Effect of Resveratrol



AMPK: Adenosine Monophosphate-Activated Protein Kinase, CCR: Chemokine 6 receptor, C/EBP: CCAAT/enhancer-binding protein, PARP :Poly (ADP-ribose) Polymerase, FAS: Fatty acid synthase, CPT: Carnitine palmitoyl transferase, FOXO1: Forkhead Box O1, ACC: Acetyl-CoA carboxylase.

Resveratrol has a wide variety of mechanisms that, when applied to many tissues, inhibit cell death and increase cell survival. It protects beta cells from damage caused by oxidative stress by preventing the cleavage of caspases and poly ADP ribose polymerase (PARP). To protect cells against necrosis, PARP inhibition stops the depletion of ATP and NAD+. Resveratrol also increases beta cell counts and inhibits chemokine receptor 6 (CCR-6) production, which in turn decreases inflammation.

Among its many anti-obesity effects, resveratrol reduces the production of adipokines, macrophage infiltration, and proinflammatory cytokines. Improving energy metabolism, it increases adipose tissue metabolism by increasing mitochondrial biogenesis and upregulating lipogenic enzymes. The activation of SIRT1 and AMPK-α phosphorylation activity is how resveratrol improves insulin sensitivity.

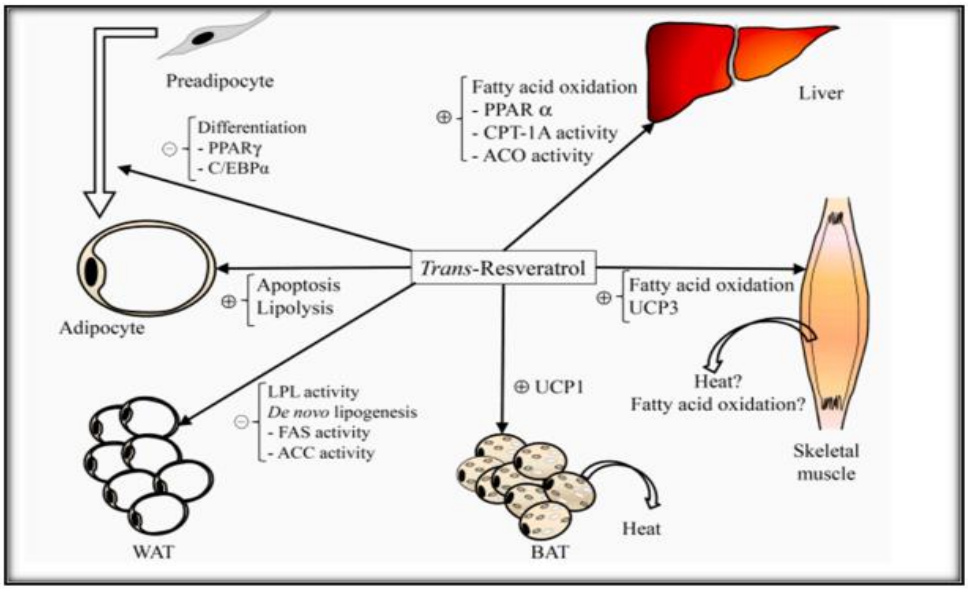
Resveratrol improves glucose transport into muscles by increasing GLUT4 expression and translocation in skeletal muscles and the liver. via lowering lipid content and eliminating insulin resistance, it controls energy metabolism via boosting mitochondrial biogenesis and

mitochondrial β-oxidation. Resveratrol activates SIRT1 in muscles, which impacts targets including PGC-1α, inflammation, and oxidative stress. This, in turn, helps with enhanced energy metabolism and insulin sensitivity.

The anti-inflammatory properties of resveratrol include blocking the action of COX-1, controlling the production of prostaglandins, and reducing levels of NF-κB and inflammatory cytokines such as IL-6 and TNF-α. Additionally, it regulates mitochondrial biogenesis, which improves energy metabolism. In addition, Akt, phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), and insulin receptor substrate-1 (IRS-1) are some of the proteins in the insulin pathway that resveratrol favourably influences.

Resveratrol's diverse mechanisms contribute to its protective effects against cell death, inflammation, and insulin resistance, positioning it as a promising therapeutic agent for various metabolic disorders.

Anti-obesogenic effect of Resveratrol



ACC: Acetyl-CoA carboxylase, ACO: Acyl-CoA oxidase, BAT: Brown adipose tissue, C/EBP: CCAAT/enhancer-binding protein, CPT: Carnitine palmitoyl transferase, FASN: Fatty acid synthase, LPL: Lipoprotein lipase, PPAR: Peroxisome proliferator-activated receptor, UCP: Uncoupling protein, WAT: White adipose tissue.

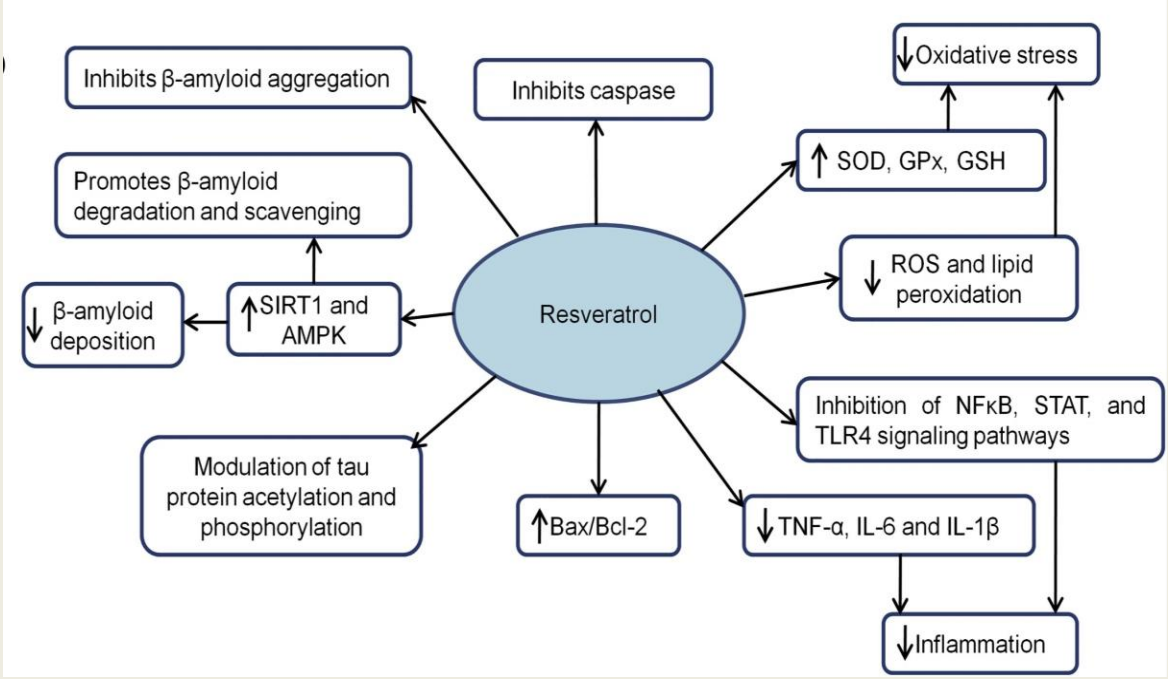
Trans-resveratrol acts on preadipocytes by inhibiting their differentiation into adipocytes through down-regulation of C/EBP and PPAR-γ proteins. This reduces lipid accumulation by decreasing cell viability and fat formation. In mature adipocytes, resveratrol activates apoptosis and lipolysis.

Moreover, resveratrol promotes the expression of the UCP1 gene in brown adipose tissue,

thereby enhancing the formation and thermogenic function of brown adipocytes, which dissipate energy as heat.

Additionally, resveratrol helps regulate de novo lipogenesis by decreasing the activity of enzymes such acetyl-CoA carboxylase (ACC), lipoprotein lipase, and fatty acid synthase (FASN). Fatty acid oxidation is promoted as a result of its notable enhancement of PPAR-α and Carnitine palmitoyl transferase activity in the liver. Similarly, it promotes fatty acid oxidation in skeletal muscle via activating the UCP3 gene.

The potential protective role of resveratrol against Alzheimer's illness



STAT: Signal Transducer and Activator of Transcription, TLR4: Toll-Like Receptor 4, AMPK: Adenosine Monophosphate-Activated Protein Kinase.

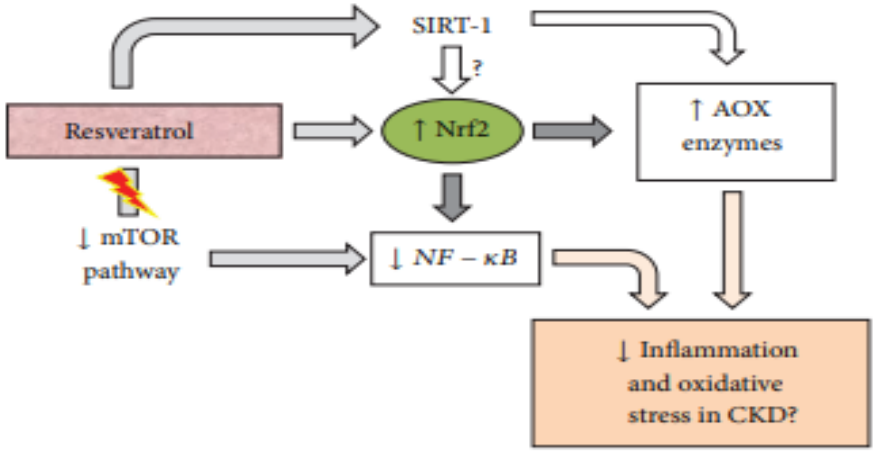
The accumulation of amyloid-β (Aβ) peptides and misfolded proteins, such tau protein, is a hallmark of Alzheimer's disease, a prevalent neurological illness among the elderly. The polyphenol resveratrol has an important role in reducing the progression of this illness *via* many pathways:

- Resveratrol increases the activity of antioxidant enzymes including superoxide dismutase and glutathione peroxidase while decreasing levels of reactive oxygen species (ROS). Lipid peroxidation drops as a result, which is another evidence of less oxidative stress.
- Resveratrol reduces inflammatory cytokine levels, such as TNF-α, IL-6, and IL-1β, which in turn lessens inflammation. Combating inflammation is achieved by targeting transcription factors and enzymes such as NF-κB and COX-2.
- Resveratrol modifies the ratio of pro-apoptotic Bax to anti-apoptotic Bcl-2 proteins and

blocks caspase-3 activation. The prevention of β-amyloid-induced apoptosis is achieved by the control of cell death mechanisms.

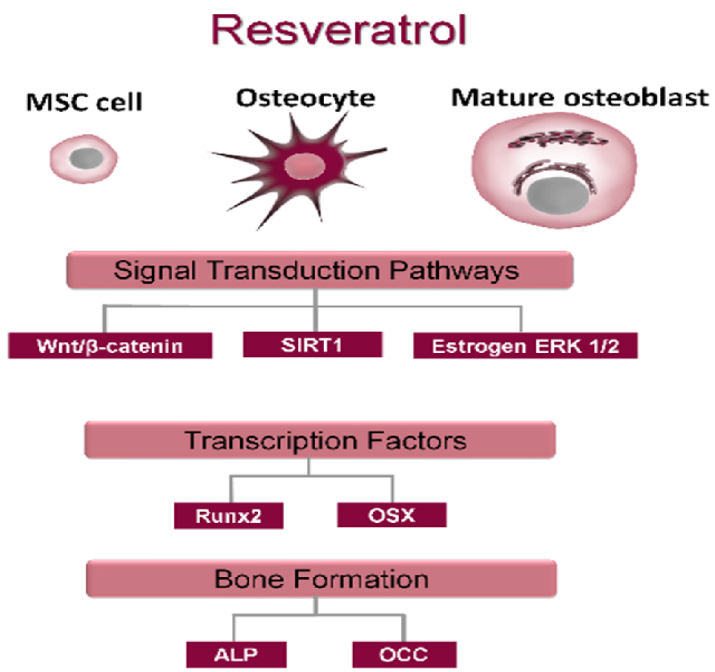
- Resveratrol helps break down and remove β-amyloid peptides by interfering with their ability to aggregate and accumulate. This step aids in reducing the buildup of harmful Aβ plaques in the brain, a characteristic of Alzheimer's disease.
- Resveratrol prevents tau misfolding and aggregation via regulating tau acetylation and phosphorylation. Resveratrol helps with Alzheimer's disease management in general by influencing tau protein pathogenesis.

Resveratrol to reduce inflammation and oxidative stress



In order to control inflammation and oxidative stress, resveratrol activates SIRT-1, blocks the mTOR pathway, and adjusts Nrf2 and NF-κB factors. This demonstrates its anti-inflammatory properties by reducing inflammation and oxidative damage.

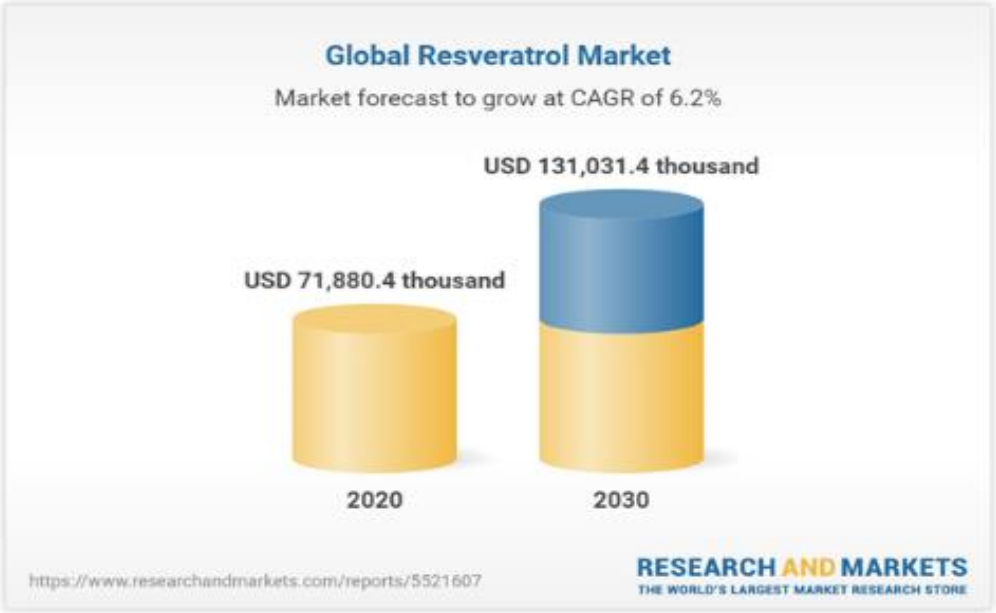
Osteogenic effect of resveratrol



ALP: Alkaline Phosphatase, OSX: Osterix, MSC cells: Mesenchymal Stem Cells, OCC: Osteocalcin, Rux2: Runt-related transcription factor 2.

The antioxidant resveratrol (RSV) promotes healthy bones by reducing the rate of bone loss and increasing the rate of bone growth. Osteoblasts are cells that produce new bone, while osteoclasts are cells that break down existing bone. It promotes the former and decreases the latter. The presence of resveratrol promotes the activation of osteoblast-related genes in several cell types, including human mesenchymal stem cells (MSCs) and osteoblastic MC3T3 cells, such as osteocalcin and osteopontin. Additionally, it influences many signalling pathways to help mesenchymal stem cells differentiate into osteoblasts.

Resveratrol increases the production of key proteins, such as RUNX2 and osterix, which are necessary for osteoblast development, via activating oestrogen receptors and the ERK1/2 pathway. In addition, resveratrol inhibits the production of osteoclasts that reabsorb bone by blocking the activity of NF-κB, which is caused by the Wnt signalling pathway and AMP-activated protein kinase (AMPK). The suppression of RANKL leads to a decrease in osteoclast differentiation. In conclusion, resveratrol promotes bone health by retaining bone mass and promoting bone formation via a number of signalling pathways that increase osteoblast activity and decrease osteoclast activity.



Global resveratrol is projected to experience a compound annual growth rate of 6.2%, reaching a value of USD 13,031.4 thousand by the year 2030.

Supplements available in market

Safety, tolerability and toxicity of resveratrol

Exceeding a daily intake of 2.5 grams can result in certain gastrointestinal symptoms. (Silva *et al.*, 2023)

Side effects includes

- Nausea
- Vomiting
- Diarrhea
- Headache, Stomach upset and Bloating

Conclusion

Resveratrol, a stilbenoid abundant in plants, holds promise for diverse therapeutic effects. However, its limited bioavailability poses challenges for pharmaceutical utilization. The absence of comprehensive preclinical toxicological studies adds complexity to research endeavors. To fully exploit resveratrol's potential in treating human diseases, novel delivery systems are essential for augmenting its biological efficacy, thereby maximizing its nutraceutical applications. So that it can be used as multi target therapeutic agent in addressing chronic disease.

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Abbreviations

ACC: Acetyl-Coa Carboxylase	LPL: Lipoprotein Lipase
ACO: Acyl-Coa Oxidase	Mnsod: Manganese-Dependent SOD
ALP: Alkaline Phosphatase	MSC Cells: Mesenchymal Stem Cells
AMPK-A: Adenosine Monophosphate-Activated Protein Kinase-A	NF-KB: Nuclear Factor-Kb
BAT: Brown Adipose Tissue	O3: Ozone
BMI: Body Mass Index	OSX: Osterix
BUN: Blood Urea Nitrogen	P38 MAPK: Mitogen-Activated Protein Kinases
C/EBP: CCAAT/Enhancer-Binding Protein	PARP: Poly ADP Ribose Polymerase
CCR-6: Chemokine Receptor 6	PGC-1α: Proliferator-Activated Receptor-Γ Coactivator-1α
CPT: Carnitine Palmitoyl Transferase	PI3K: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase
Cr: Creatininea	PPAR: Peroxisome Proliferator-Activated Receptor
DBP: Diastolic Blood Pressure	PGC-1α: Proliferator-Activated Receptor-Γ Coactivator-1α
FASN: Fatty Acid Synthase	PI3K: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase
FBS: Fasting Blood Sugar	PPAR: Peroxisome Proliferator-Activated Receptor
FOXO1: Forkhead Box O1	Rux2: Runt-Related Transcription Factor 2
Gamma-Gt: Gamma-Glutamyl Transpeptidase	SBP: Systolic Blood Pressure
Hb: Hemoglobin	SIRT1: Sirtuins
Hba1c: Hemoglobin A1c	STAT: Signal Transducer and Activator Of Transcription,
HDL: High Density Lipoprotein	STS: Stilbene Synthase
HO: Heme Oxygenase-1,	TNF-A: Tumor Necrosis Factor-A
IKB: Inhibitor Of KB	TL4: Toll-Like Receptor 4
IL-1β: Interleukin-1β	UCP: Uncoupling Protein
IUPAC :International Union Of Pure And Applied Chemistry	VEGF:Vascular Endothelial Growth Factor
LDL: Low Density Lipoprotein	WAT: White Adipose Tissue