UNLOCKING THE THERAPEUTIC POTENTIAL OF RESVERATROL

Divya, C [1], Raju,C.A[2] and Mamatha, H.S.[3]

[1,2]PhD Scholar
Department of Food Science and Nutrition
University of Agricultural Sciences, Bangalore-560056
[3]Associate Professor
Department of Food Science and Nutrition
University of Agricultural Sciences, Bangalore-560056

Abstract: Resveratrol, (3,4′,5-trihydroxy-trans-stilbene) a polyphenolic compound classified under the stilbene group, emerges as a secondary metabolite in over 70 plant species in response to environmental challenges. 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.

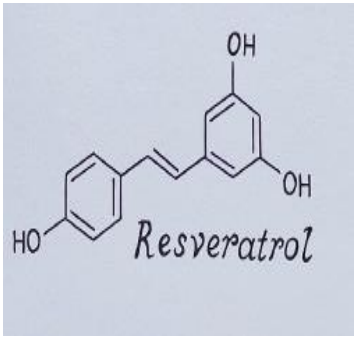
Key words: Resveratrol, Metabolism, Molecular mechanism,Therapeutic potential, Saftey,Tolerability

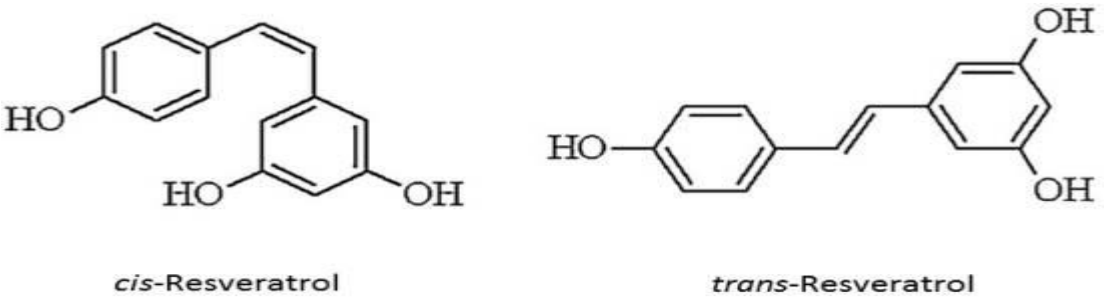
History

- Resveratrol (3,4′,5-trihydroxy-*trans*-stilbene) was first isolated in 1939 by **Takaoka** from ***Veratrum grandiflorum* O**.
- In **1963**, from the roots of Japanese knotweed.
- In **2004**, Harvard University professor **David Sinclair** co-founded **Sirtris** Pharmaceuticals, and formulated resveratrol.

Introduction

Resveratrol is a secondary metabolite belongs to a class of polyphenolic compounds called stilbenes**,** produced in more than 70 plant species in response to environmental stress, such as mechanical injury, microbial infection, and UV irradiation. Resveratrol is named as 5-[(E)-2-(4-hydroxyphenyl) ethenyl] benzene-1,3-diol (IUPAC).Two phenol rings are linked by a methylene double bond to generate 3,5,4 -trihydroxystilbene Resveratrol exists in nature in two isomeric forms (Figure 1): trans-resveratrol and cis-resveratrol.Although both isomers are biologically active, a majority of biological functions of resveratrol are attributable to trans resveratrol, which is the more stable form.

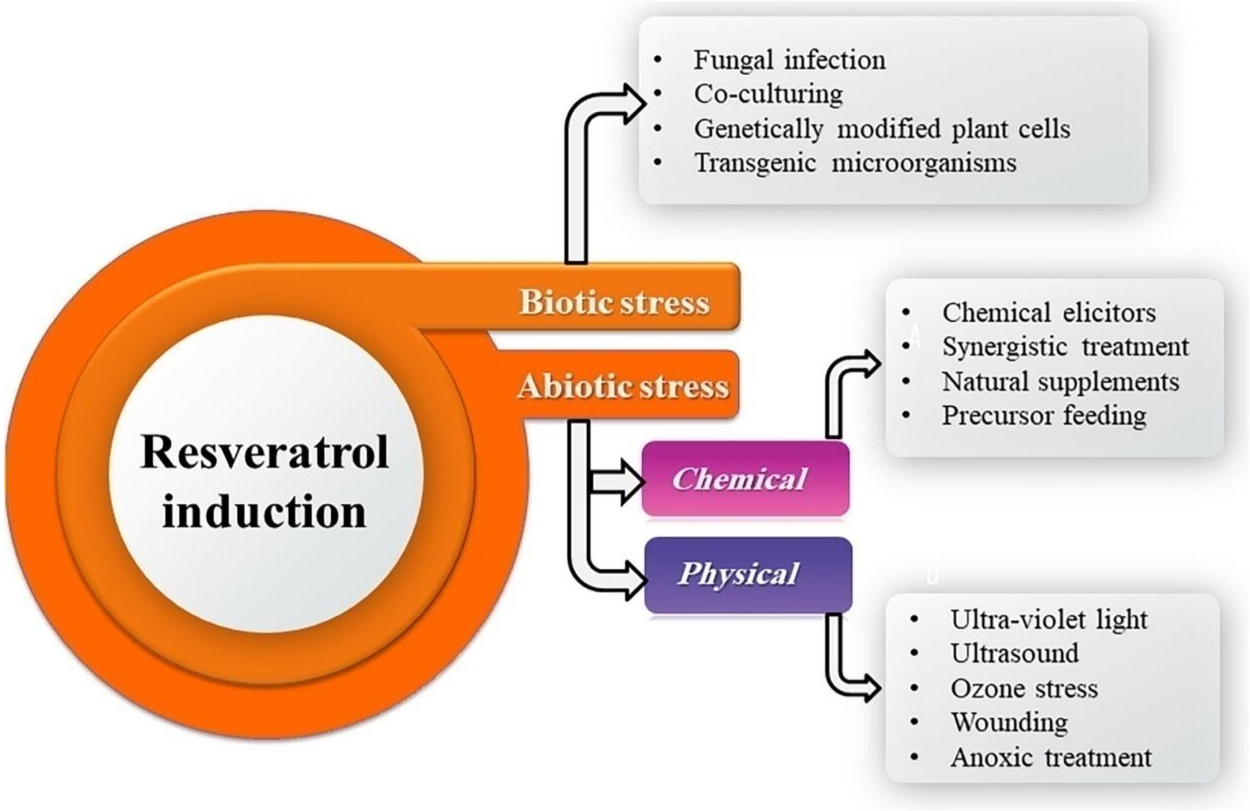




cis-Resveratrol *trans*-Resveratrol

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.

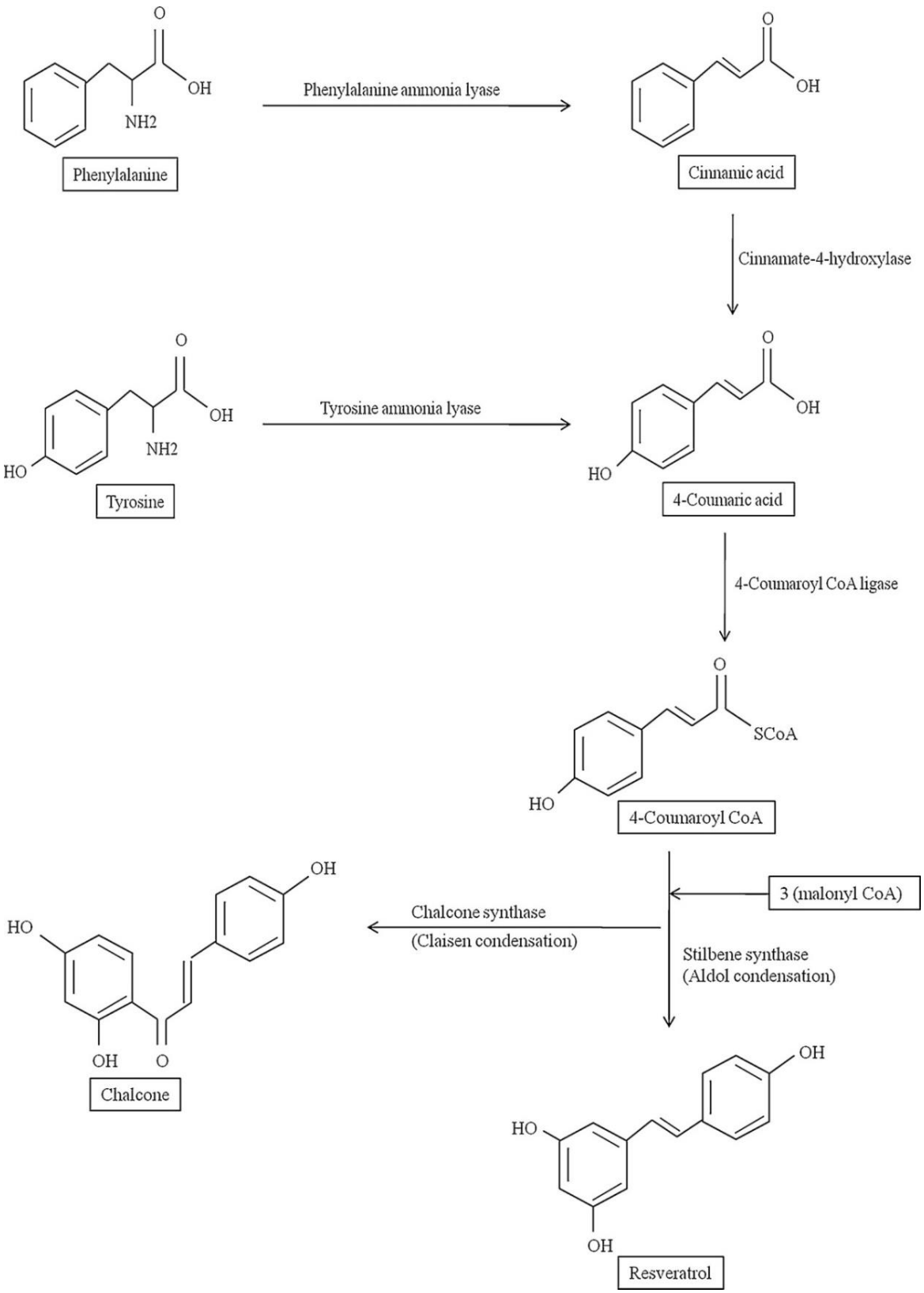
Physical properties of resveratrol

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

The chemical formula of resveratrol is $C_{14}H_{12}O_3$ with molecular weight of 228.25 g/mol. It appears as a white powder with a slight yellow cast. it has a boiling point range of 253 to 255°C. In terms of solubility, it is sparingly soluble in water (0.03 g/L), moderately soluble in ethanol (50 g/L), and soluble in dimethyl sulfoxide (16 g/L). Other names for resveratrol include trans-3,5,4-trihydrozystilbene, 3,4,5-stilbenetriol, (E)-5-(p-hydroxystyryl) resorcinol, 3,5,4'-trihydroxy-cis-stilbene, and 3,5,4'-trihydroxy-trans-stilbene.

Bio-synthesis of Resveratrol

Resveratrol is synthesised in plants by the phenylpropanoid pathway, in response to external stimuli such as UV radiations, microbial infection, fungicides, etc, and is therefore a secondary metabolite. For the synthesis of resveratrol the phenylpropanoid pathway involves aromatic amino acids L-phenylala- nine and L-tyrosine . The non-oXidative deamination reaction of these amino acids by L-phenylalanine ammonia lyase and L- tyrosine ammonia lyase leads to the generation of cinnamic acid and 4- coumaric acid, respectively. Cinnamic acid is eventually converted to 4- coumaric acid by hydroXylation reaction catalysed by cinnamate-4- hydroXylase. Conversion of 4-coumaric acid to 4-coumaroyl-CoA by the enzyme 4-coumaroyl CoA ligase generates an active intermediate. Condensation of 4-coumaroyl-CoA with malonyl-CoA and its cyclisation eventually leads to the generation of the stilbene, resveratrol. This step is catalysed by the enzyme 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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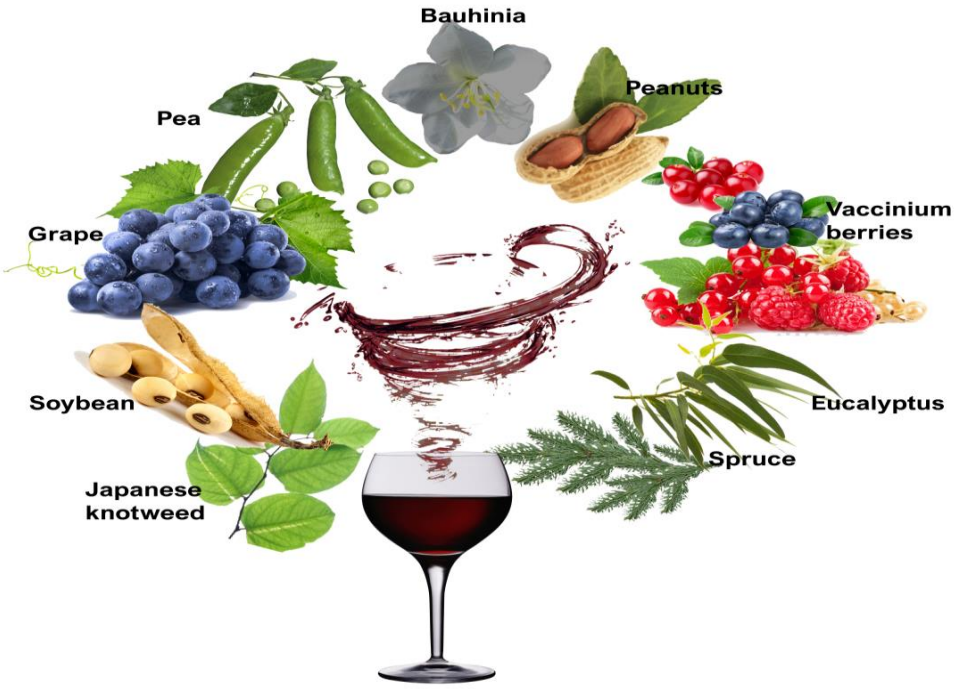
Sources/Occurance



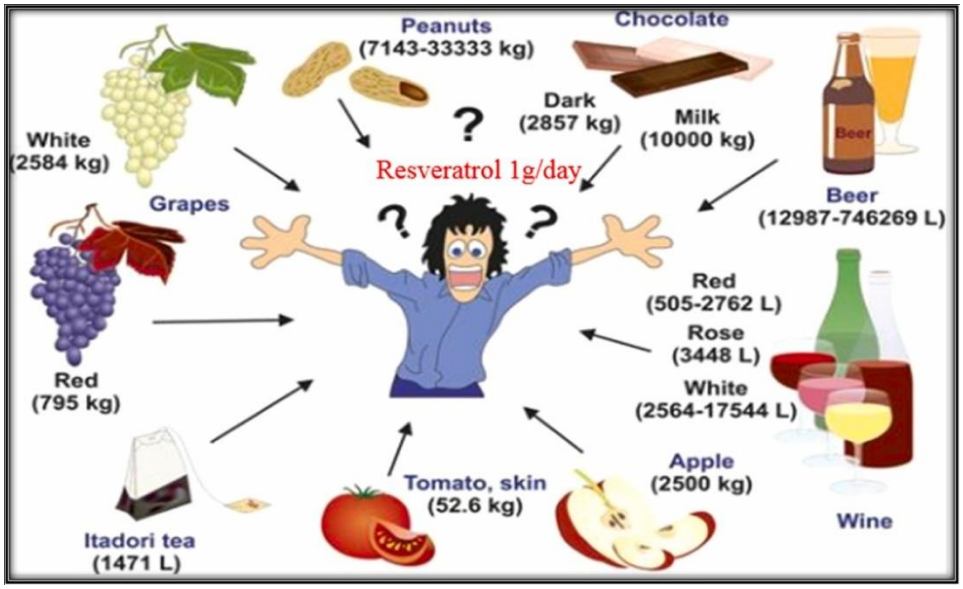
Major sources include peanuts (*Arachis hypogaea*), grapes (*V. vinifera*) and grape products (must, wine), soybean (*Glycine max*), pea (*Pisum sativum*), berries (*Vaccinium* spp.), Japanese Knotweed (*Fallopia japonica*), spruce (*Picea excelsa*), bauhinia (*Bauhinia racemosa*), and eucalyptus (*Eucalyptus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

List of Resveratrol sources with its concentration

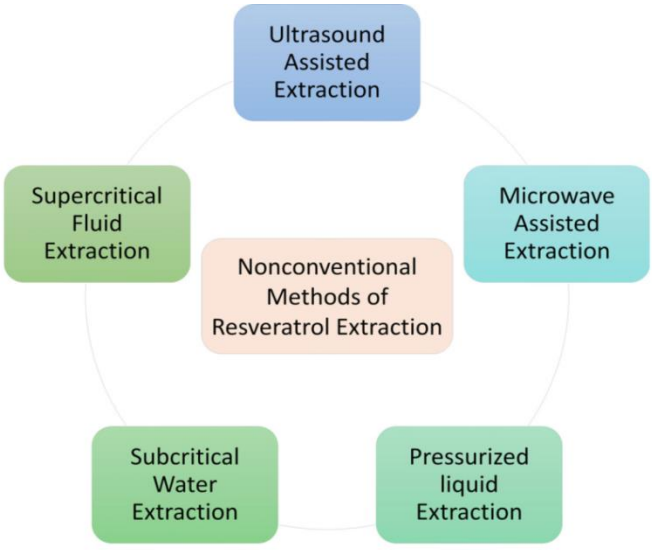
Sources	Resveratrol
Wine	0.32-15.35 µg/g
Peanut butter	0.02-0.98 µg/g
Peanuts	0.01-0.07 µg/g
Green peanuts	0.19-0.72 µg/g
Polygonum cuspidatum	296-377 µg/g
Green grapes	0.02-0.32 µg/g
Black grapes	0.95-1.88 µg/g
Raisins	0.0005-0.003 µg/g
Grape juice-black	Traces-0.09 µg/g
Grape juice-green	Traces-0.01 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

The richest natural sources of resveratrol are dark grape extracts (*Vitis vinifera*) and giant knotweed (*Polygonnum cuspidatum*, a perennial shrub). It is also found in abundance in labrusca and muscadine grapes. It is also present in other plants such as Eucalyptus, spruce and lily and in foods such as mulberries, peanuts, blueberries, strawberries, hops and their products

The number of beverages and foods that must be consumed to achieve a therapeutic dose will vary. If a person tries to consume 1 g of RESVERATROL per day, the consumed amount of food and drink is depicted in below figure.



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 is used as a solvent, at temperatures between 100 and 374ºC and pressure high enough to maintain the liquid state.

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.

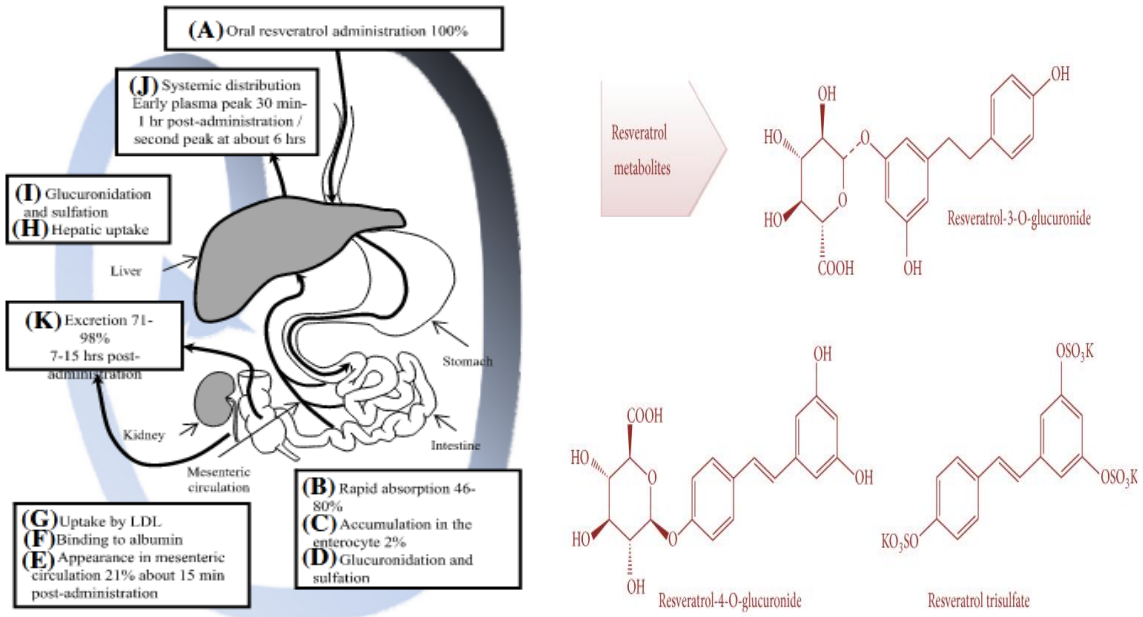
Pressurized liquid extraction (PLE): PLE, also known as accelerated solvent extraction (ASE), is an extraction technique that operates under high temperature and pressure.

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, obtained from food or supplements, is rapidly absorbed(46-80%) in the small intestine. In the intestine, it undergoes glucuronidation and sulfation catalyzed by

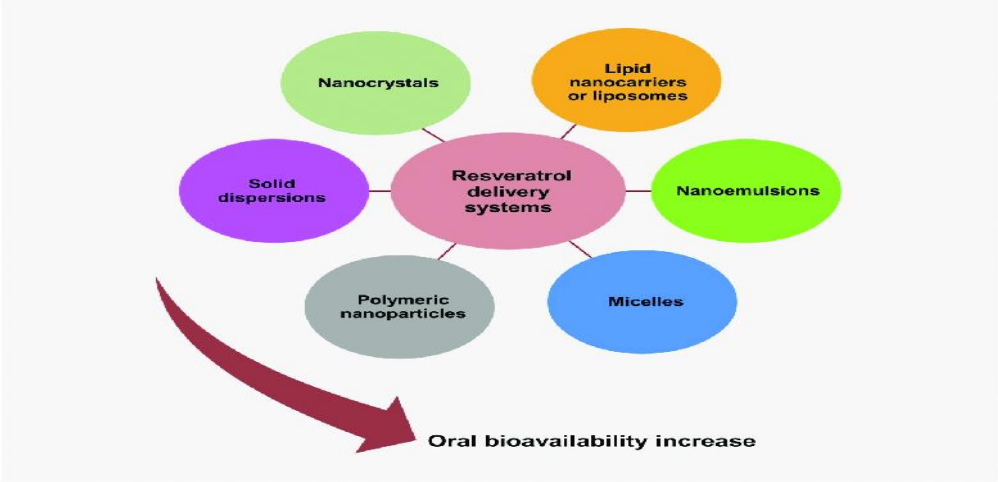
glucuronosyltransferases and sulfotransferases. Metabolites of resveratrol are absorbed through active transport and bind to albumin and lipoproteins in the bloodstream. These complexes act as reseResveratroloirs, facilitating distribution to cells by dissociating when they reach cells with albumin and lipoprotein receptors.

Resveratrol reaches the liver via 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



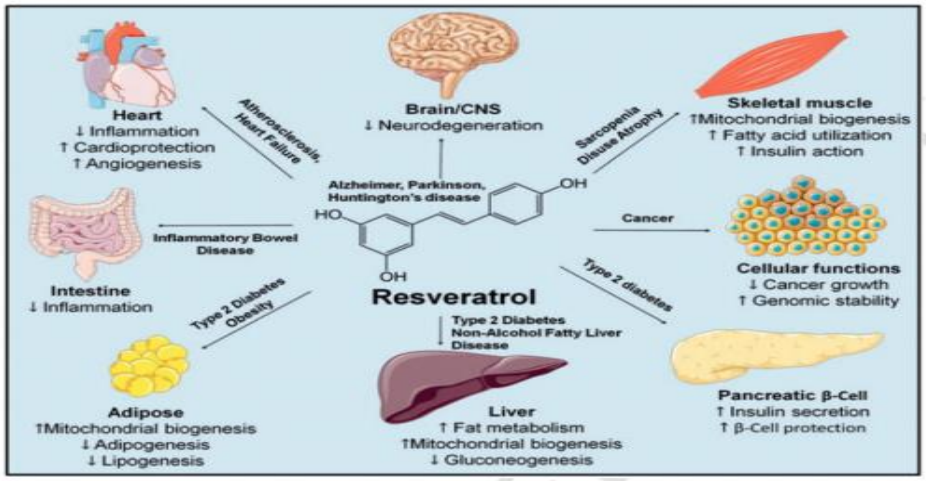
Enhancing the oral bioavailability of resveratrol is crucial for maximizing its therapeutic efficacy. Various effective strategies include nanoformulation, nanoparticle delivery, nanoemulsions, solid dispersions, micelles, and nanocrystals.

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.

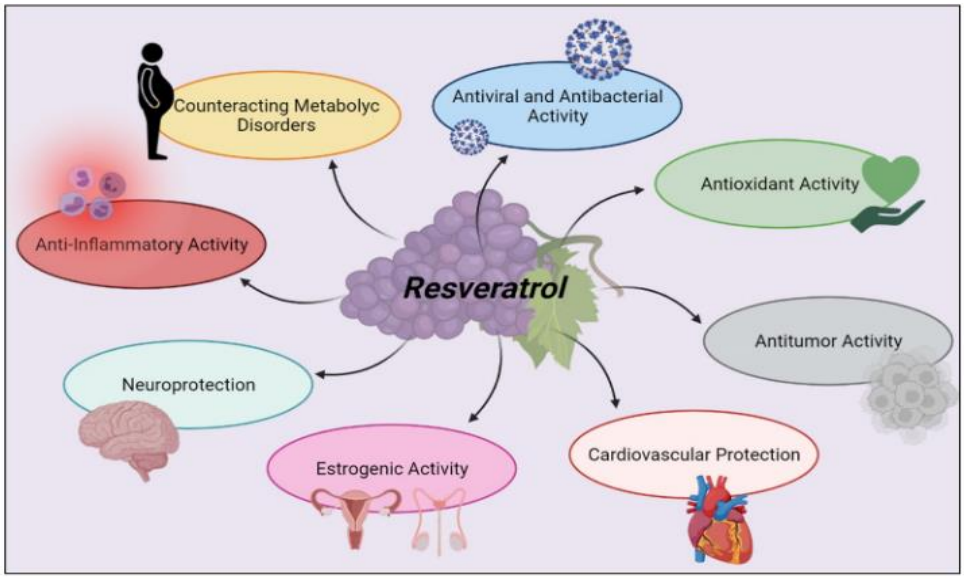
Another method is dispersing resveratrol within a polymeric matrix to boost its solubility and dissolution rate, thereby enhancing absorption. Utilizing Solid Lipid Nanoparticles can also safeguard resveratrol from degradation and improve absorption through enhanced lipid solubility.

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



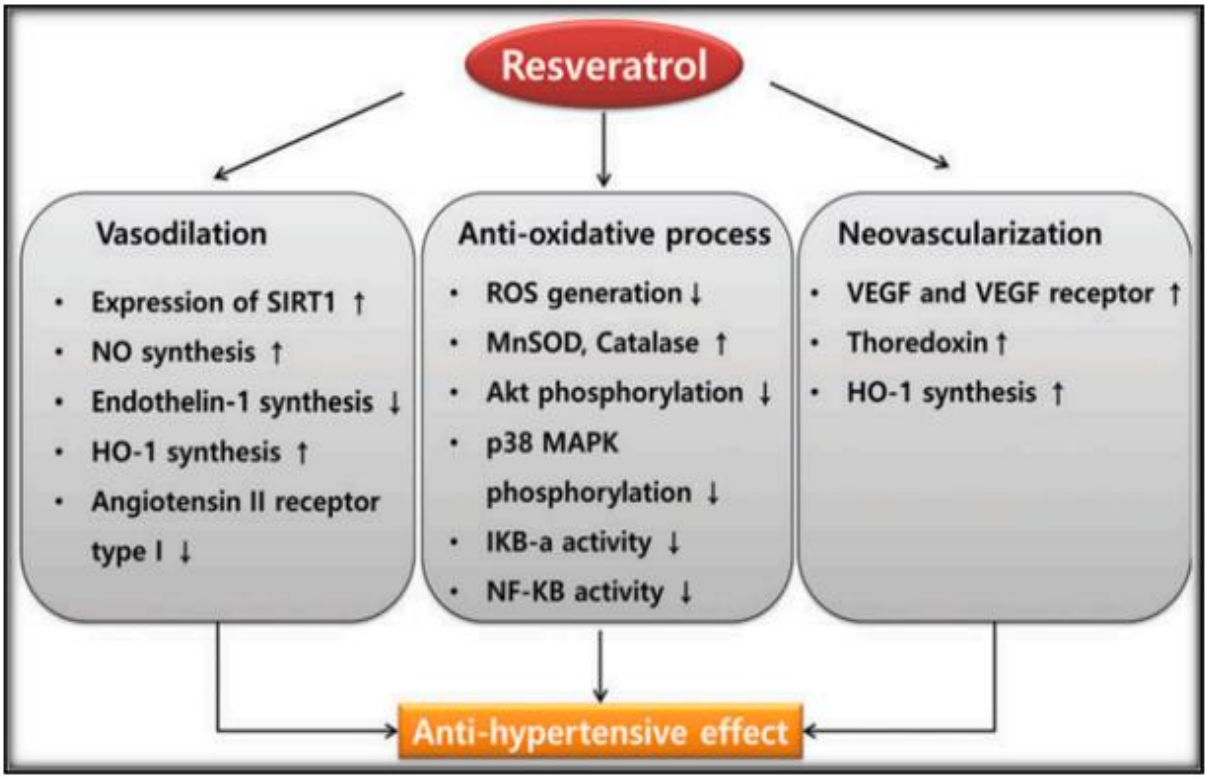
BIOLOGICAL PROPERTIES



Resveratrol exerts a wide range of health benefits 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



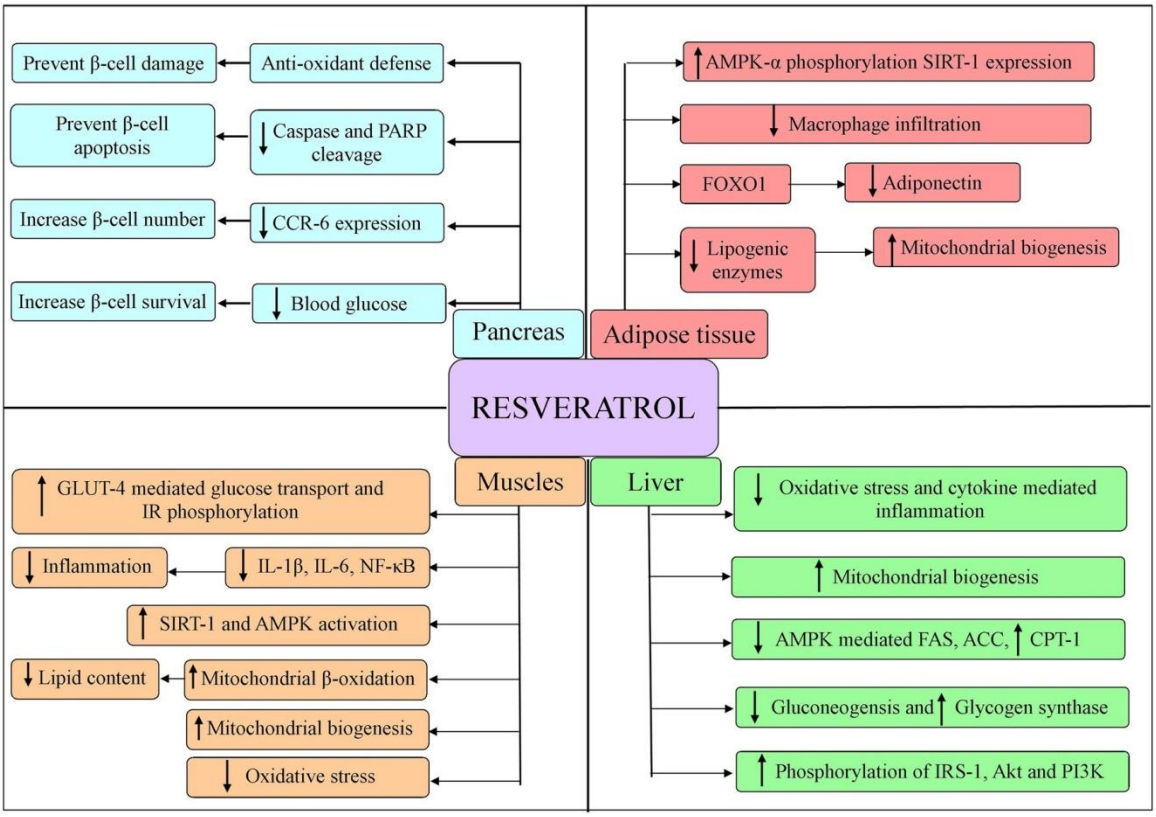
Resveratrol exhibits its blood pressure-lowering effects through various mechanisms, including vasodilation, antioxidative actions, and neovascularization. It primarily targets SIRT1 and sirtuins, leading to vasodilation by upregulating endothelial nitric oxide production. This also enhances the synthesis of heme oxygenase-1 (HO-1), a precursor to bilirubin, exerting an antihypertensive effect.

Moreover, resveratrol reduces the expression of angiotensin II receptors and endothelin synthesis, both of which are vasoconstrictors. Its antioxidative properties involve suppressing reactive oxygen species (ROS) production, Akt phosphorylation, and the activities of p38 MAPK, IKB, and NF-KB, while increasing the levels of manganese superoxide dismutase (MnSOD) and catalase.

Furthermore, resveratrol promotes neovascularization by increasing the expression of vascular endothelial growth factor (VEGF) and its receptors, along with enhancing

thioredoxin production to regulate redox reactions and maintain cellular homeostasis. Additionally, it stimulates the synthesis of HO-1, which possesses anti-inflammatory effects.

Antidiabetic Effect of Resveratrol



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

Resveratrol demonstrates multifaceted mechanisms in preventing cell death and promoting cell survival across various tissues. Its antioxidative properties counteract oxidative stress-induced beta cell damage by inhibiting caspases and poly ADP ribose polymerase (PARP) cleavage. Inhibition of PARP prevents ATP and NAD+ depletion, safeguarding cells from necrosis. Additionally, resveratrol inhibits chemokine receptor 6 (CCR-6) expression, mitigating inflammation and increasing beta cell numbers.

In combating obesity-related inflammation and insulin resistance, resveratrol reduces proinflammatory cytokines, macrophage infiltration, and adipokine release. It enhances adipose tissue metabolism by upregulating lipogenic enzymes and increasing mitochondrial

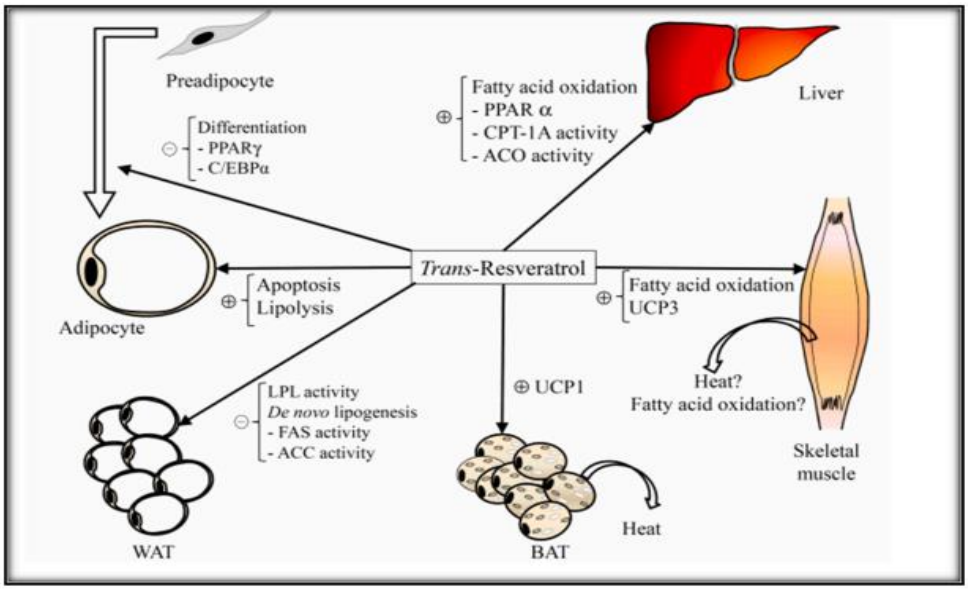
biogenesis, consequently improving energy metabolism. Furthermore, resveratrol enhances insulin sensitivity by activating SIRT1 and adenosine monophosphate-activated protein kinase-α (AMPK-α) phosphorylation activity.

In skeletal muscles and the liver, resveratrol enhances GLUT4 expression and translocation, facilitating glucose transport into muscles. It regulates energy metabolism by promoting mitochondrial biogenesis and enhancing mitochondrial β-oxidation, reducing lipid content and overcoming insulin resistance. SIRT1 activation by resveratrol in muscles influences targets like peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), inflammation, and oxidative stress, further contributing to improved energy metabolism and insulin sensitivity.

Resveratrol's anti-inflammatory effects extend to inhibiting COX-1, regulating prostaglandin synthesis, and suppressing NF-κB and inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). It also enhances energy metabolism by regulating mitochondrial biogenesis. Moreover, resveratrol positively affects downstream insulin pathway proteins such as insulin receptor substrate-1 (IRS-1), Akt, and phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K).

Overall, resveratrol's diverse mechanisms contribute to its protective effects against cell death, inflammation, and insulin resistance, making it a promising therapeutic agent in various metabolic disorders.

Anti-obesogenic effect of Resveratrol



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

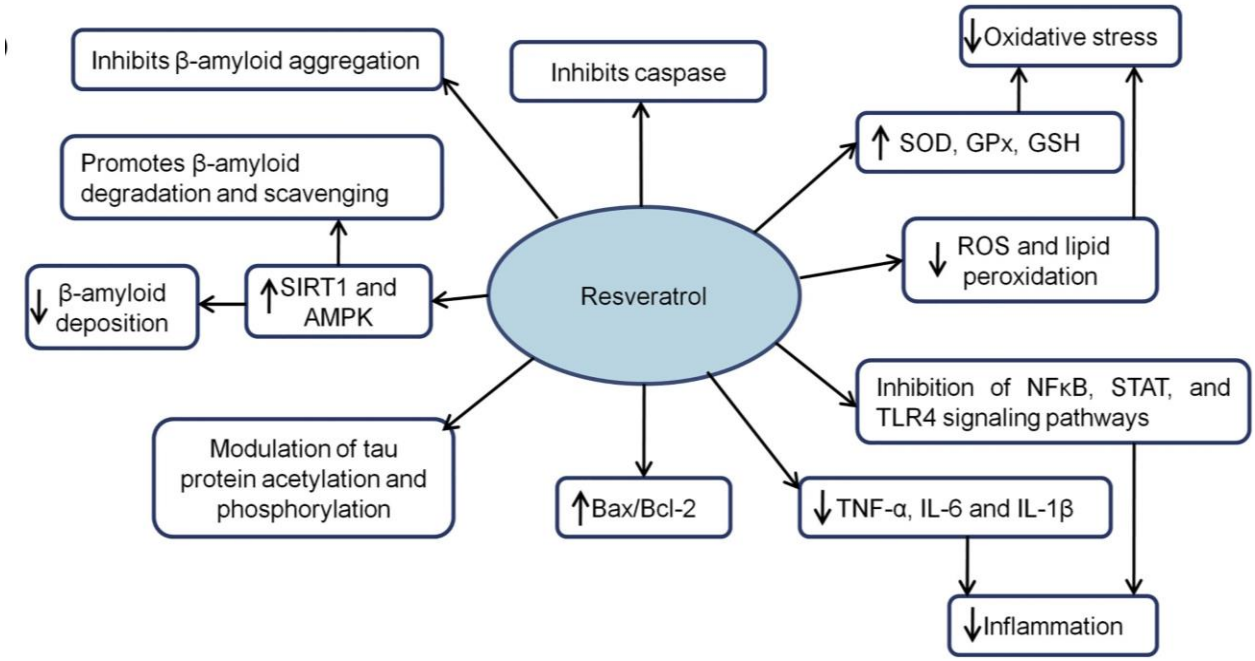
Trans-resveratrol acts on preadipocytes by inhibiting their differentiation into adipocytes

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.

Resveratrol also reduces the effects of enzymes such as Lipoprotein lipase, Fatty acid synthase (FASN), and Acetyl-CoA carboxylase (ACC), thus aiding in controlling de novo lipogenesis. It significantly improves the activity of PPAR-α and Carnitine palmitoyl transferase in the liver, promoting fatty acid oxidation. Similarly, in skeletal muscle, it activates the UCP3 gene, facilitating fatty acid oxidation.

Protective effect of resveratrol on Alzheimer's disease



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

Alzheimer's disease is a prevalent neurodegenerative condition among the elderly, characterized by the accumulation of amyloid-β (Aβ) peptides and misfolded proteins like tau protein. Resveratrol, a polyphenol, plays a crucial role in mitigating the progression of this disease through various mechanisms:

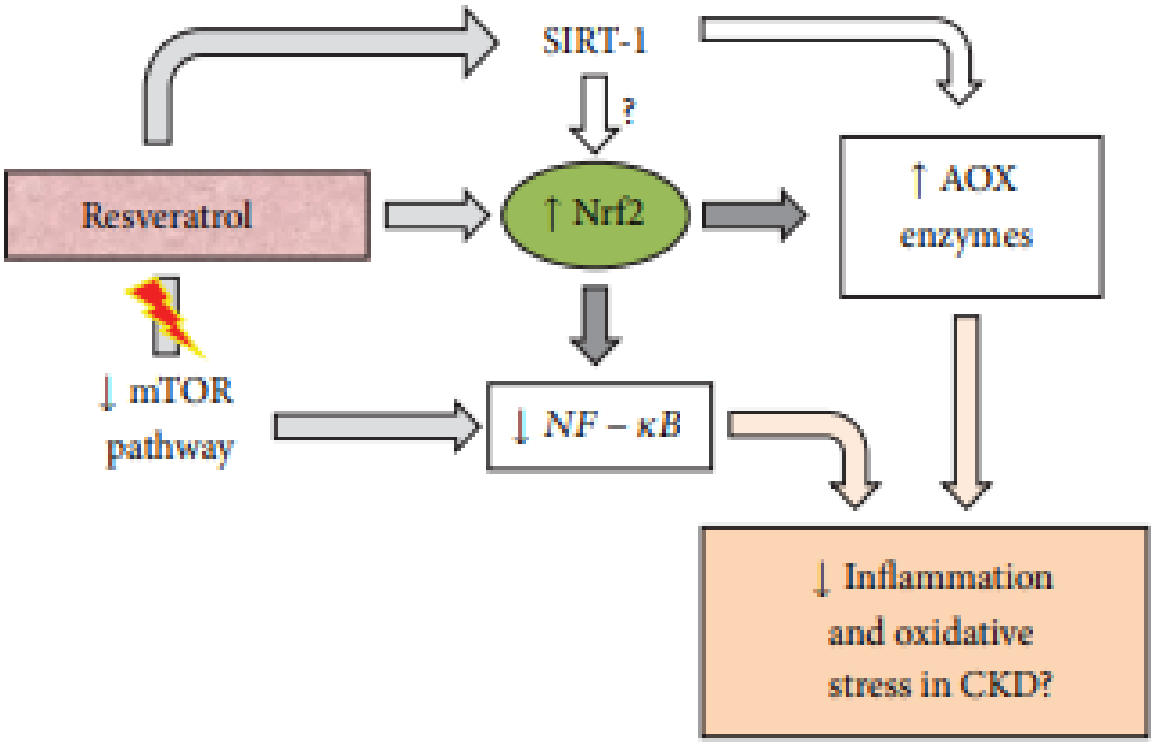
- **Reduction of Oxidative Stress**:Resveratrol inhibits the levels of reactive oxygen species (ROS) and boosts the activity of antioxidant enzymes such as glutathione peroxidase and superoxide dismutase. This leads to decreased lipid peroxidation,

confirming a reduction in oxidative stress.

- **Resveratrol decreases inflammation** by reducing the levels of inflammatory cytokines like TNF-α, IL-6, and IL-1β. It also targets transcription factors and enzymes like NF-κB and COX-2, thereby combating inflammation.

- Resveratrol inhibits caspase-3 activity and adjusts the balance between pro-apoptotic Bax and anti-apoptotic Bcl-2 proteins. This inhibition of cell death pathways helps prevent β-amyloid-induced apoptosis,
- **Inhibition of β-Amyloid Aggregation and Deposition**:Resveratrol disrupts the aggregation and deposition of β-amyloid peptides, facilitating their degradation and clearance. This action helps mitigate the accumulation of toxic Aβ plaques in the brain, a hallmark of Alzheimer's disease.
- **Resveratrol regulates the acetylation and phosphorylation of tau protein**, preventing its misfolding and aggregation. By modulating tau protein pathology, resveratrol contributes to the overall management of Alzheimer's disease.

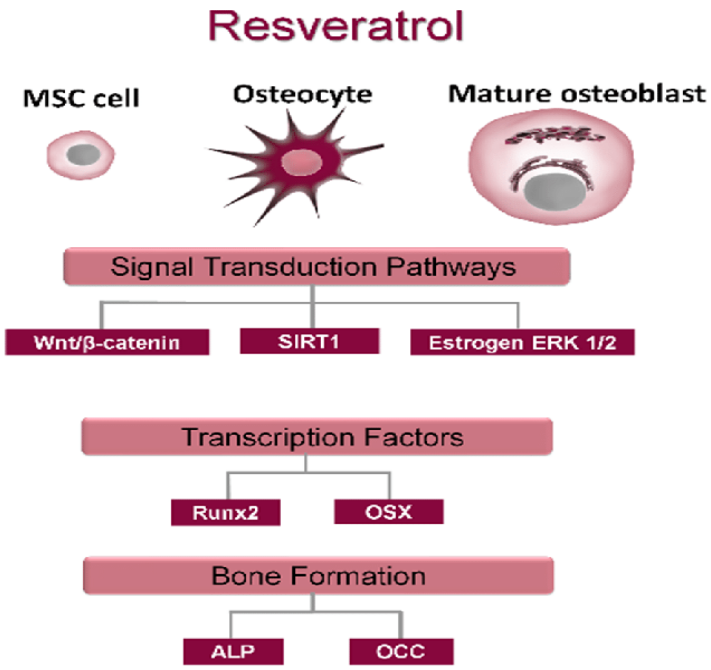
Resveratrol to reduce inflammation and oxidative stress



Resveratrol helps to manage inflammation and oxidative stress by activating SIRT-1,

inhibiting the mTOR pathway, and modulating Nrf2 and NF-κB factors. This action leads to reduced inflammation and oxidative damage, showcasing its anti-inflammatory effects.

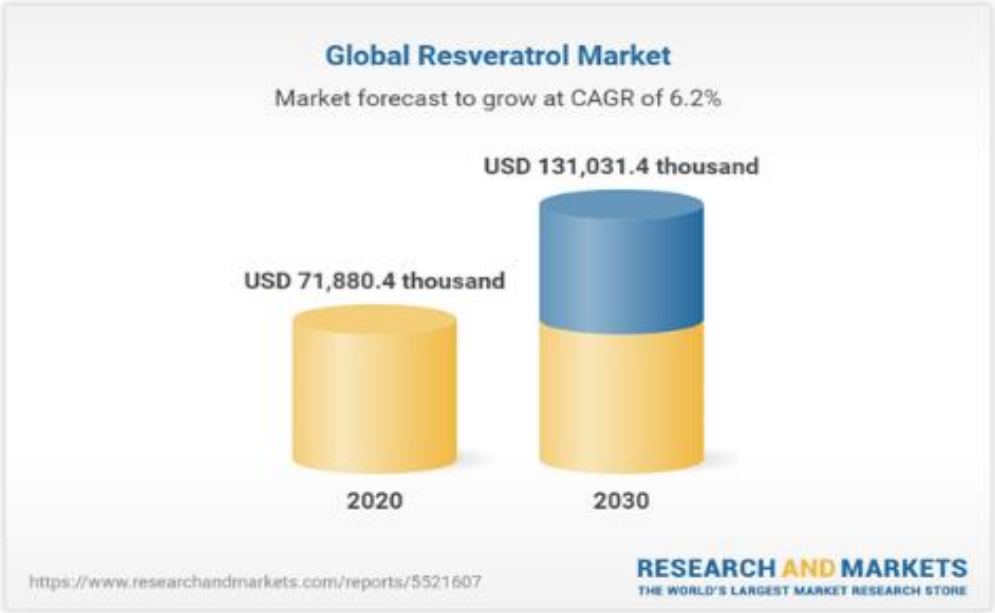
Osteogenic effect of reservatrol



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

Resveratrol (RSV) positively affects bone health by boosting bone formation and reducing bone breakdown. It encourages the production of bone-building cells (osteoblasts) and suppresses the activity of bone-resorbing cells (osteoclasts).RSV promotes the expression of genes associated with osteoblasts, such as osteocalcin and osteopontin, in various cell types including human MSCs and osteoblastic MC3T3 cells. It also aids in the differentiation of mesenchymal stem cells into osteoblasts by influencing several signaling pathways.By activating estrogen receptors and the ERK1/2 pathway, RSV enhances the expression of key factors like RUNX2 and osterix, crucial for osteoblast formation.
Additionally, RSV activates the Wnt signaling pathway and AMP-activated protein kinase (AMPK), which together inhibit the formation of bone-resorbing osteoclasts by blocking NF-κB activity. This inhibition leads to a decrease in osteoclast differentiation induced by RANKL.Overall, resveratrol aids bone health by promoting osteoblast activity and suppressing osteoclast activity through various signaling pathways, ultimately supporting

bone formation and preserving bone mass.



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

Above 2.5 g per day can lead to some adverse gastrointestinal symptoms (Silva *et al*.,2023)

Side effects

- 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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ABBREVATIONS

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