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Resveratrol: An Outstanding Natural Compound With Broad Biomedical Applications

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ABSTRACT— In 1939, the Japanese scientist Michio Takaoka first mentioned resveratrol from Veratrum grandiflorum O. Loes. Majority of plants, such as grapes, berries, and peanuts, are significant sources of resveratrol, a well-known polyphenolic. resveratrol (RV) is noted for its links to several health care benefits, including glucose metabolism, anti-aging, cardioprotective, neuroprotective, antitumor, antidiabetic, and antioxidant effects. Importantly, there have been reports of promising therapeutic qualities in atherosclerosis, dementia, and various malignancies. These properties are controlled through a number of cooperative techniques, which control inflammation besides the effects of oxidative stress and cell death. However, circulating resveratrol is rapidly broken down, according to pharmacokinetic study data. It prompts questions regarding the physiological significance of the high concentrations commonly employed in in vitro studies. To find out if resveratrol or its metabolites accumulate in tissues, further investigation is needed.

KEYWORDS: Resveratrol, Veratrum grandiflorum O. Loes, and Phenol or polyphenolic product.

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1. INTRODUCTION

One of the many complex biological phenomena associated with aging is the slow degradation of physiological systems, which increases the risk of disease and ultimately results in death. Researchers are concentrating more on finding novel ways to prevent aging, promote skin health, and improve general quality of life as the world's population continues to age [1].

In 1940, it was initially discovered in the white hellebore root (Fig. 1). Alternatively known as Varaire (Veratrum grandiflorum), this plant species thrives at elevations of 1000 meters and above throughout the majority of mountain ranges in central and southern Europe, the Caucasus, temperate Asia, Siberia, and even as far away as Japan. Takaoka discovered resveratrol (3,5,4′-trihydroxystilbene), A polyphenol compound that appears naturally [2].

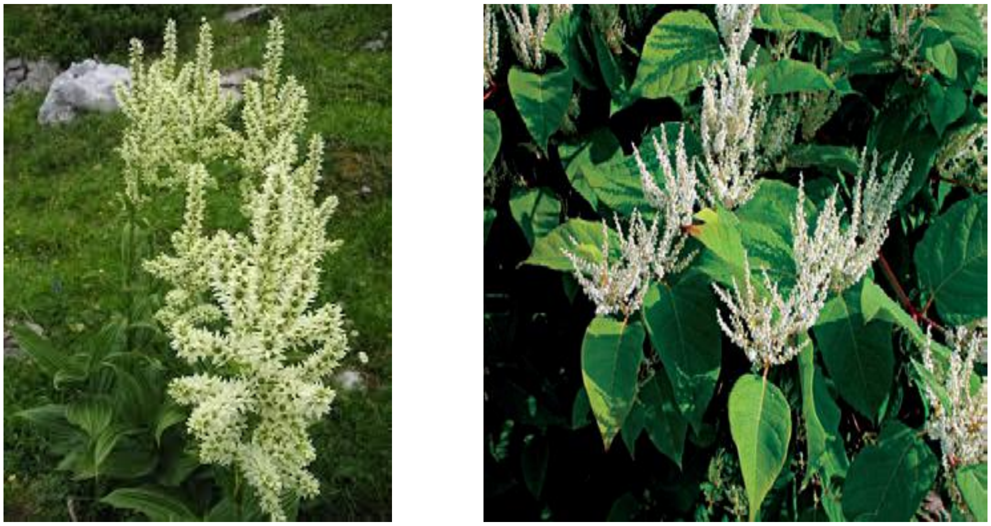

Fig 1. Veratrum grandiflorum as the first source of Resveratrol

Resveratrol's possible health advantages, which are abundant in foods like blueberries, strawberries, and grapes, have garnered a lot of interest. Resveratrol has been shown in studies to promote mitochondrial health, fight oxidative stress, inhibit inflammatory pathways, and affect cellular apoptosis. It seems to have dose-dependent anti-aging and anti-inflammatory effects (3).

Resveratrol has shown promise in randomized controlled trials and animal studies, along with other noteworthy substances like metformin, rapamycin, and NAD+ precursors, suggesting its potential importance for tackling human aging (4).

It has the dual benefits of lowering oxidative stress and inflammation, which helps organisms of various species live longer (5). Better blood glucose and insulin resistance in diabetes (6) and obesity prevention (7) have been demonstrated in recent studies.

Resveratrol (8) may influence the NF-kB pathway, control the immune system's reaction to infections, and control how cells react to stimuli. Furthermore, the IGF-1R/Akt/Wnt pathways can be inhibited, and the cancer process and cellular development may be impacted by activated P53 signaling (9).

Additionally, resveratrol has the ability to suppress the PI3K/Akt, as it acts to control growth, proliferation, cell differentiation, and other processes that control these processes, as well as several other activities (10). Numerous studies have shown many ways that RV affects the PI3K/Akt pathway. For instance, RV may be highly beneficial in treatment when combined with other PI3K/Akt/mTOR inhibitors since it has been shown to block Akt in Multicellular carcinomas and their signaling, exhibiting hyperactivation of the mechanism of rapamycin (mTOR) PI3K/Akt (11). Strong antioxidant activity and elevated nitric oxide (NO) generation may be linked to the RV compound's probable cardioprotective properties (12).

Resveratrol has been demonstrated to lower hepatic lipid synthesis and may also prevent platelet aggregation, which can effectively prevent human polymorph nuclear leukocytes from producing reactive oxygen species (ROS) (13). and is thought to be a stronger antioxidant than vitamin E (14).

Additionally, it has been demonstrated that resveratrol is the most efficient in blocking a wide range of foodborne infections, suggesting that it might be used as an alternative to ensure the superior quality,

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advantageous items that are unquestionably safe to consume (15).

2. Histological background about Resveratrol.

Initially found in the white hellebore root in 1940, resveratrol, additionally referred to as 3,4',5 trihydroxy-trans-stilbene, is a naturally occurring polyphenol (Fig. 2) that belongs to the stilbene group. Also known as Varaire (Veratrum grandiflorum), this plant species is found in Siberia, the Caucasus, central and southern Europe, temperate Asia, and even as far away as Japan (2).

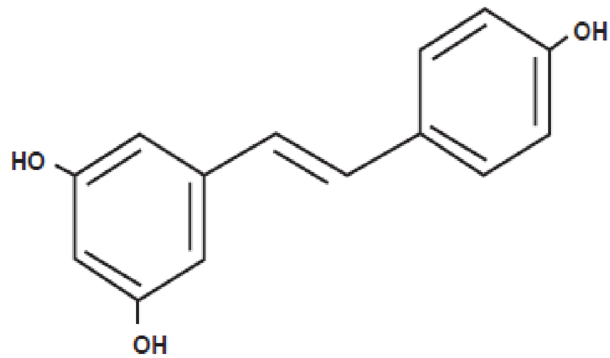

Fig. 2 Resveratrol chemical structure.

The Japanese knotweed (Polygonum cuspidatum), which has been utilized in traditional Chinese (Hu-Chang) and Japanese (Ko-jo-kon) medicine since 2000 BC, has also been found to contain significant amounts of resveratrol in its roots (16). The root of the *Polygonum* is currently the main source of natural resveratrol on the market. The vineyard was found to contain resveratrol in 1976 by Langcake and Pryce. They described it as a phytoalexin, which means a defense molecule of the plant. In reaction to biotic infections, such as those brought on by the fungus Botrytis cinerea, the vine produces resveratrol, which is responsible for “gray decay” in grapes, a widespread disease well-known to winemakers. In response to abiotic stressors like UV radiation or ozone exposure, the vine also produces phytoalexin (17).

3. Resveratrol

Natural materials have been used extensively to treat human illnesses throughout history. The correlation between quinine and cinchona and salicylates and willow is a well-known example. The fabled discovery of penicillin is comparable (18). Resveratrol has long been used in Chinese and Japanese medicine due to its numerous medicinal advantages. Over 70 plant species contain resveratrol, a naturally occurring polyphenolic antioxidant that belongs to the stilbene family (19).

Two aromatic rings connected by a methylene bridge comprise the majority of RV's chemical structure. It can be defined as a white powder that is low in weight and is extracted using methanol. Its melting point ranges from 253 to 255 ◦C. In nature, RV exists in both trans- and cis-isomeric forms. (Fig. 3) (20).

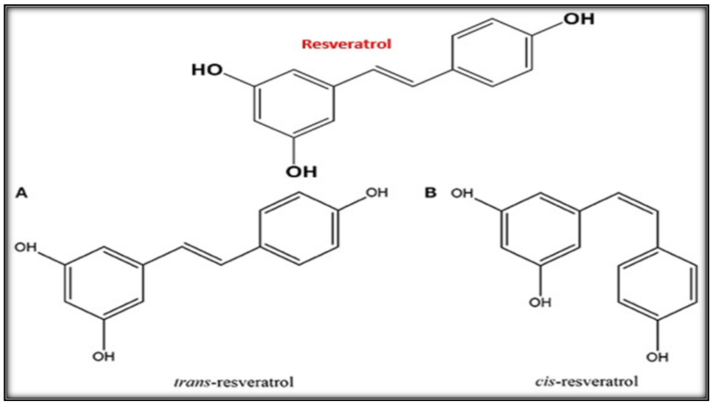

Fig. 3 Resveratrol and its enzymatic structures (A) trans-RV (B) cis-RV

The outer layer of peanuts, red grapes, pistachios, pomegranates, mulberries, blueberries, bilberries, soybeans, cranberries, and soy are common sources of RV (Fig. .4). These foods are frequently used in RV supplements. Non-food plants, including certain kinds of grass, flowers, and pine bark, can also produce RV (21).

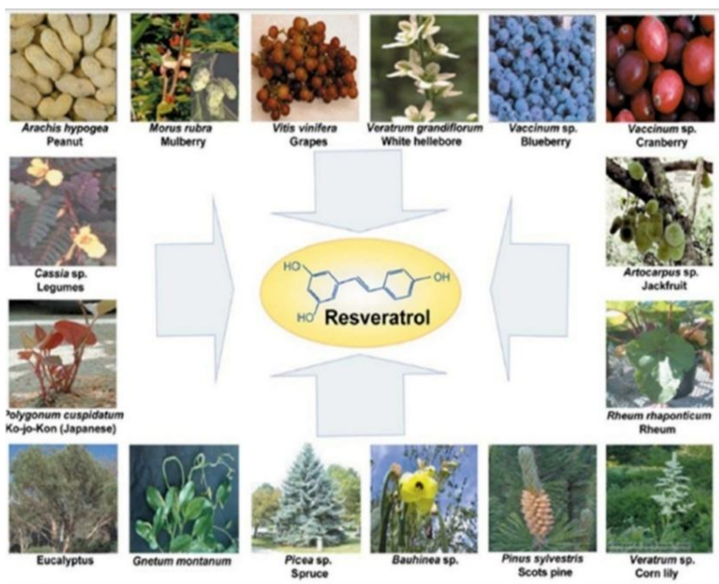

Fig. 4 Different sources of Resveratrol

4. Resveratrol and its reliable actions

Resveratrol inhibits SIRT1/3 activity, which in turn stimulates the AMPK signaling pathway and decreases the amount of acetylation of SOD2 and ROS produced by the enzyme NOX4 (nicotinamide adenine dinucleotide phosphate oxidase) (22). Resveratrol stimulates the vintages, activates SIRT1, and can lengthen the dendritic length and density of the spine. It also inhibits the activity of the brain's carbonyl protein (23). Additionally, it reduces the effect of the rotenone gene of the homologous protein C/EBP (CHOP) and glucose regulatory protein 78 (GRP 78) on the endoplasmic reticulum (ER) (23). Resveratrol inhibits phosphorylation of Protein kinase, Jun N-terminal kinase (JNK), and the release of matrix metalloproteinases (MMP)-2 and -9 (24).

Resveratrol inhibits the synthesis of NOX and myeloperoxidase while positively correlated with the synthesis of thioredoxin, SOD, catalase, and GPx (peroxidized glutathione peptide). It has been determined that RV reduces oxidative stress, which makes it seem to directly absorb free radicals from tissues. (25), (26).

Resveratrol helps purify a peptide, cleave the amyloid precursor protein in an anti-amyloidogenic manner, make the protein resistant to oxidative stress, and cause brain-associated cells to die. Thus, RV can be defended as a crucial method for improving AD medication treatment. (27). Inhibiting inflammatory markers (IL-6, TNF-α, Cxcl10, Ccl3, IL-1) and oxidative stress were two more important functions of resveratrol (28).

5. Resveratrol utilization approaches.

5.1 Resveratrol and Skin Aging.

A complicated series of events, skin aging is a reflection of both extrinsic and natural age changes. The cellular and molecular mechanisms of natural aging are comparable to those of extrinsic or photoaging, but the clinical stigmata are very different. Enhanced production of reactive oxygen species (ROS) in situ, as they arise from acute stress reactions to various environmental stressors, including UV radiation, as well as a disruption of mitochondrial activity, is thought to be the main factor contributing to skin aging. (29).

Additionally, Strong evidence suggests that the depletion of naturally occurring antioxidants, which serve as a protective mechanism against damage from free radicals, is linked to both intrinsic and extrinsic skin aging (30). ROS can directly harm proteins, DNA, and cell membranes if they are not controlled. Furthermore, ROS stimulates cellular and molecular mechanisms that accelerate skin aging, such as the upregulation of transcription factors like activator protein 1 (AP-1) and nuclear factor-kB (NF-kB) (31). Among the primary transcription factors responsible for producing the collagen-degrading enzymes called metalloproteinases (MMPs) is AP-1, an important feature that has shown that MMPs play a crucial role in accelerating premature skin aging (32). According to in vitro research, resveratrol has a crucial function in maintaining dermal collagen and lowering skin inflammation by efficiently downregulating both AP-1 and NF-kB (33). Resveratrol shares a stilbene chemical structure with diethylstilbesterol, a synthetic estrogen. Resveratrol's phytoestrogen and estrogen beta receptor agonist (ERβ) properties are therefore not surprising (34).

Clinical indicators of skin aging are improved, and collagen degradation is lessened with estrogen replacement therapy. Because phytoestrogens like resveratrol may offer the skin advantages of estrogen without the hazards, their application is particularly intriguing. Additionally, resveratrol may be used to lighten skin. Resveratrol and other stilbenes have been shown to exhibit strong tyrosinase inhibitory action in studies (35).

5.2 Resveratrol as an Antioxidant.

The strongest antioxidant activity of resveratrol is arguably its most well-known characteristic. This polyphenol's dual antioxidant capability is one of its most unique characteristics. Resveratrol encourages the synthesis of additional naturally occurring enzymatic antioxidants within cells. Specifically, nuclear factor-E2-related factor-2 (Nrf2), a transcription factor that regulates multiple genes involved in reactive oxygen species detoxification, is upregulated when resveratrol is present (36).

It has been demonstrated to increase the intracellular antioxidant capacity by boosting naturally occurring enzymatic antioxidants such as hemoxygenase-1, catalase, and superoxide dismutase (37).

Pure resveratrol's well-established direct free radical scavenging capabilities seem to be significantly influenced by the hydroxyl group's structural location (38). The last way that resveratrol prevents lipid peroxidation is by chelating copper and working with antioxidants like vitamin E (39).

5.3 Antidiabetic roles.

Increased hyperglycemia from gluconeogenesis and increased hepatic absorption of glucose are hallmarks of diabetes, a widespread and potentially fastest-growing metabolic disease worldwide (40).

Herbs can offer this beneficial therapy alternative since other treatments still need to check for adverse effects, even though anti-hyperglycemic medications and insulin sensitizers are crucial (41).

In rats, it was discovered that RV increases insulin and decreases blood glucose while decreasing drug-resistant genes (Streptozotocin + Nicotinamide); consequently, insulin sensitivity was enhanced. Moreover, RV impacted the hemeoxygenase 1 (HO-1) and retinal Nrf2 genes (42). Researchers found that RV could considerably boost capillary development and density while also lowering blood glucose and TG values. Additionally, the Nrf2 and HO-1 gene normalization and transcript levels were progressively reversed. Accordingly, the results suggested that RV could reduce blood sugar and cholesterol, preserve vascular endothelial cells from the wound caused by diabetes, and regulate Nrf2/HO (43). Traditional herbs have acquired appeal due to their good effects on the hypoglycemic perspective, as well as the fact that they have few side effects, according to recent observations (44). Therefore, it has been noted that RV, a naturally occurring polyphenol, has strong effects on reducing the amount of gluten in the diet and stopping the hydrolysis of carbohydrate-enzyme activity (45).

5.4 Pharmacokinetics of resveratrol

The effectiveness of RV in the bloodstream following the production of glucuronide conjugates and its easy blood-brain barrier crossing, which is a subject of extensive research. As a result, it plays a significant part in the management of neurodegenerative illnesses such as HD, AD, PD, and ALS (46). Numerous studies have demonstrated the neuroprotective effects of resveratrol at doses between 10 and 100 μM. Alzheimer's disease is a long-term neurodegenerative illness that causes cognitive and behavioral abilities to gradually decline. (47).

Several oligomers, dimers, and monomers have been identified. For instance, it has been discovered that two new stilbene dimers, ε-glucoside with residual glucose and Syrupin with extra-OH groups, have a potent inhibitory effect on the accumulation of fibrillar material. They can therefore be used to treat AD as fibrillation inhibitors (48). Scirpus A and ε-viniferin glucosides are examples of RV derivatives that can be used as effective therapeutic and preventative agents to help prevent neurodegenerative diseases like Alzheimer's disease, and some of the most promising anti-neurodegenerative properties have also been demonstrated by their derivatives (49).

6. Conclusion

A stilbenoid is widely available in the herbal world; resveratrol has several potential medical benefits, for example, anti-inflammatory, anti-carcinogenic, antioxidative, and anti-cardioprotective elements.

Although it has historically been used to treat skin inflammation, hepatitis, arthritis, fungal diseases, abdominal pain, and urinary tract infections, RV's primary biological promise is cardio protection, anti-cancer, and neuroprotective. Numerous cancer types are believed to be preventable and treatable with resveratrol, as it shows ultimate actions towards these medical defects. Numerous in vitro and in vivo investigations have verified RV's anticancer qualities, demonstrating that it can block carcinogenesis at every step.

Resveratrol has many positive effects; its poor oral solubility and absorption are a big worry. Due to its considerable hepatic glucuronidation and sulfation, resveratrol has a low bioavailability. More research is needed to determine resveratrol's therapeutic potential in humans fully. To determine the optimal dosages, long-term safety, and the full range of its benefits, comprehensive clinical trials are necessary.

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