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THE PROMISING THERAPEUTIC EFFECTS OF RESVERATROL: A REVIEW OF HUMAN CLINICAL STUDIES

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ABSTRACT: Resveratrol (3, 5, 4′-trihydroxy stilbene) is a type of natural phenol, produced by several plants in response to injury or under attack by pathogens. These phytoalexin compounds are thought to have antioxidant, anticancer, and anti-inflammatory properties. Although resveratrol is commonly used as a dietary supplement, there is no conclusive evidence of whether or not resveratrol could be a viable treatment in humans. Despite the richness of *in-vitro* and *in-vivo* research, which confirms its potential therapeutic effects, there is insufficient clinical evidence on its beneficial results in humans. In this review, we have focused on the mechanism of action of resveratrol and on clinical trials that have evaluated the efficacy of reseveratrol in cancer, cardiovascular diseases and neurodegenerative disorders.

INTRODUCTION: There is considerable interest in the therapeutic potential of natural products because of their low toxicity and minor side effects. Plant-derived polyphenolic compounds have recently attracted a lot of research interest throughout history, due to their antioxidant properties and potential pharmacological effects [1]. One of the most widely studied polyphenols is Resveratrol. Resveratrol (3, 4′, 5- trihydroxy stilbene) is a small phenolic compound that is produced naturally by several plants when they become attacked by bacterial or fungal pathogens (phytoalexin) [2, 3]. Resveratrol is a member of the stilbene family (two benzene rings linked via isopropyl moiety separated by a double bond), which exists as *cis* and trans stereoisomers (Z and E) with the transform exhibiting the principal form found [4, 5] **Fig. 1**.

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Resveratrol is found in various food and food products such as grapes, peanuts, wine, grape juice, berries, and various other plants. It was first isolated in 1940 from the roots of white hellebore (Veratrumgrandiflorum O. Loes) [6] **Fig. 2** and later in 1963, from the roots of Polygonumcuspidatum, a plant used widely in traditional Chinese and Japanese medicine [7] **Fig. 3**. Resveratrol attracted little interest until 1992 when it was proposed to explain some of the cardioprotective effects of red wine [8]. The presence of resveratrol in red wine at high concentrations (0.1–14.3 mg/L) suggested explaining the interesting "French Paradox" which suggested an unexpectedly low rate of heart disease among Southern French people who consume a lot of red wine, despite their diets being high in saturated fat [9, 10].

Since then, several reports have been conducted to evaluate the effect of resveratrol in the prevention and treatment of various diseases and medical illnesses [11, 12, 13, 14, 15, 16]. From a pharmacokinetic perspective, results indicate that in spite of rapid absorption circulating resveratrol is rapidly undergo intestinal and hepatic metabolism *via*

glucuronic acid and sulfates [17]. The produced conjugates accumulate in plasma and urine, thus resulting in poor bioavailability of the compound. Also, the high lipophilicity of resveratrol leads to low aqueous solubility, which may potentiate its poor oral bioavailability [18]. Accordingly, resveratrol has proven to be more effective when applied topically rather than administered orally [19]. Resveratrol is considered to be a relatively non-toxic and well-tolerable agent. It is reported that doses up to 450 mg/day are safe dose for a 60 kg person. Among its few dose-independent adverse effects are nephrotoxicity and gastrointestinal problems [20]. However, higher doses of resveratrol are reported to be toxic. The toxicity is thought to be due to the effect of resveratrol on several hepatic enzymes, where CYP3A4, CYP2C9, and CYP2D6 are inhibited while CYP1A2 is induced. Also, high doses of resveratrol may interact with many other drugs [21]. Thus, orally administered high doses could be risky for the patients taking several medications. In this review, we have focused on the mechanism of action of resveratrol and on clinical trials that have evaluated the efficacy of reseveratrol in cancer, cardiovascular diseases, and neurodegenerative disorders.

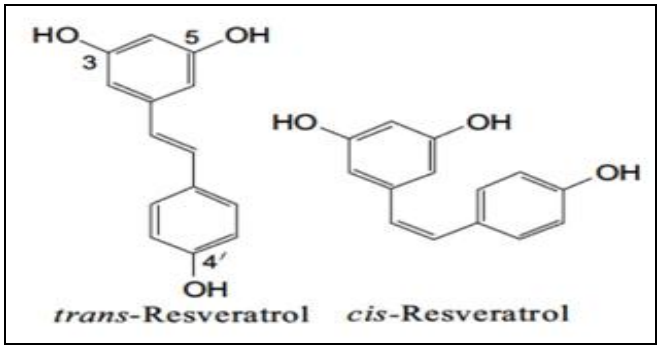

FIG. 1: CHEMICAL STRUCTURE OF RESVERATROL

FIG. 2: *VERATRUM GRANDIFLORUM O. LOES*

FIG. 3: *POLYGONUM CUSPIDATUM*

1. Mechanism of Action of Resveratrol: Resveratrol has received a great deal of attention as a probable treatment of several human diseases. The mechanism by which resveratrol exerts its favorable effects across different disease models is not yet clear, but it seems that it can act on a number of molecules in the body.

One of the suggested mechanisms that resveratrol acts as a potent antioxidant by inhibiting reactive oxygen species (ROS) generations. This is achieved mainly by activating 5' AMP-activated protein kinase (AMPK). This makes resveratrol as a potent antioxidant capable of preventing oxidative stress.

Therefore, it can explain its actions such as anticancer [22, 23,] and cardioprotective agent [24]. Resveratrol is also found to act as an inhibitor for vascular cell adhesion molecules (VCAM) expression and to influence the activity of vascular smooth muscle cells which are involved in the development of atherosclerosis and high blood pressure (hypertension), respectively [25].

Also, resveratrol exhibit an ant platelet effect through inhibiting early signaling events in Washed platelets *in-vitro* but has little effect on platelet aggregation in whole blood. Thus, although resveratrol may function as a protective agent of coronary heart disease, its effects are not solely

attributed to its effects on platelets in circulation [26]. Resveratrol also suppresses COX-2 enzymes, which are responsible for the conversion of arachidonic acid into prostaglandins. The inhibition of this pathway reduces inflammation and suggests the possibility of resveratrol as a treatment for inflammatory conditions [27]. Resveratrol is also an activator of SIRT1, a member of the sirtuin family of proteins [28]. SIRT1 deacetylates proteins, including transcription factors. This regulated pathway is therefore expected to benefit several conditions such as abnormal metabolic control, cell cycle defects, and inflammation [29, 30]. Resveratrol affects the nuclear factor κB (NF-κB) signaling pathway, which regulates inflammation, the immune response to infection, and cellular response to stimuli [31]. In addition, it has been shown to significantly inhibit the IGF-1R/ Akt/Wnt pathways and activate p53, and therefore can influence its anti-cancer activities [32].

2. Medical uses of Resveratrol:

2.1. Resveratrol and Anti-Cancer Activity: Cancer remains a chronic health problem with a high mortality rate to date. In 1997, Jang *et al.* published a research article reported the ability of topical f resveratrol in reducing the number of skin tumors up to 98% in mice 33. These findings triggered research on resveratrol on cancer treatment worldwide. Several *in-vitro* research studies on the effect of resveratrol on cancer treatment have been reported.

These studies showed that *in-vitro* resveratrol interacts with multiple molecular targets, and has positive effects on the cells of breast [34], skin [35], gastric [36], colon [37], esophageal [38], prostate [39] and pancreatic cancer [40] and leukemia [41]. Clinical studies, on the other side, must determine if the same effects can be seen in human patients.

However, few results of human clinical trials for the effect of resveratrol on cancer have been reported [42]. Reason behind this limited number of clinical trial is the pharmacokinetics of resveratrol, where it was concluded that even high doses of resveratrol might be insufficient to achieve resveratrol concentrations required for the systemic prevention of cancer [43]. This poor systemic bioavailability limits clinical trial for resveratrol on humans for the treatment of cancers [44].

The strongest evidence of anti-cancer action of resveratrol exists for tumors it can come into direct contact with, such as skin tumors [45]. For other cancers, the evidence is uncertain, even if massive doses of resveratrol are used.

2.1.1. Prostate Cancer: The few clinical trials that have been conducted show that resveratrol has several targets within the cell, and its efficacy is dependent on the type and stage of cancer, dosage levels, and treatment periods. Among the clinical trials conducted, a phase 1 clinical study was conducted on 14 subjects to describe the effect of pulverized muscadine grape skin (MPX) extract, which contains resveratrol in appreciable concentration on prostate-specific antigen (PSA) doubling time. Every 500 mg of MPX has 4.4μg of trans-resveratrol. Length of the trial was 2-35 months depending on the patient's condition. Results showed a delay in prostate-specific antigen (PSA) doubling time by 5.3 months; however, these results were not statistically significant ($P = 0.17$) [46]. The results for prostate cancer was confirmed by another randomized placebo-controlled clinical study, which was conducted using two doses of resveratrol (150 mg or 1,000 mg resveratrol daily) for 4 months. This study concluded that resveratrol could not treat prostate cancer as it had no effect on the prostate volume or PSA levels [47].

Another double-blind, randomized, placebo-controlled trial was conducted to examine the effects of the specific phytotherapeutic intervention (containing turmeric, resveratrol, green tea, and broccoli sprouts) on 22 men with recurrent prostate cancer. Patients were randomized to either the active treatment arm or placebo for 12 weeks. Results found that there is no statistical difference between groups on PSA doubling time in this study [48]. From these studies, it seems unlikely that resveratrol will prove to be an effective treatment for prostate cancer, but more clinical trials need to be performed to confirm this.

2.1.2. Colorectal Cancer: In a clinical trial conducted in patients with colorectal cancer, the results seem promising. Twenty patients with histologically confirmed colorectal cancer consumed eight daily doses of resveratrol at 0.5 or 1.0g 8 days before surgical resection. Cell proliferation, as

reflected by Ki-67 (proliferation marker) staining, was compared in preintervention and post-intervention tissue samples. Results revealed a reduction of 5% in the rate of cellular proliferation in colorectal cancer tissue [49]. Also, another phase 1 randomized, double-blind pilot study conducted on 9 patients with colorectal cancer showed activation of apoptosis and an increase in cleaved Caspase-3 level (apoptotic marker), which suggest the beneficial effect of resveratrol on colon cancer [50].

2.1.3. Breast Cancer: Alternatively, in breast cancer, a randomized double-blinded clinical trial was conducted over 12 weeks on 39 adult women at increased breast cancer risk. These women were randomized in a double-blind fashion to placebo, 5, or 50 mg trans-resveratrol twice daily for 12 wk.

Results found that the resveratrol affected the epigenetic pattern of RASSF-1α, a gene associated with breast cancer, and this effect correlated with the levels of circulating resveratrol [51]. These results suggest that resveratrol may act as a chemo preventive agent for breast cancer by influencing the epigenetics of breast cancer-associated genes, a finding that needs to be confirmed in future clinical trials. Another pilot study was conducted on postmenopausal women with high body mass index to determine the clinical effect of resveratrol on estrogen hormones, which play a main role in breast cancer. Results showed that a daily 1 gm dose of resveratrol has favorable effects on estrogen metabolism thus may have a good effect on breast cancer reduction [52].

2.1.4. Skin Cancer: In a study conducted by Farris et al. (2014), a topically applied blend containing 1% resveratrol, 0.5% baicalin, and 1% vitamin E was applied to the skin of patients with mild to moderately photodamaged skin for 12 weeks.

Findings showed a statistically significant improvement in fine lines and wrinkles, skin firmness, skin elasticity, skin laxity, hyper-pigmentation, radiance, and skin roughness after 12 weeks compared to baseline [53]. A summary of these clinical studies on a human for each cancer type is presented in **Table 1**.

TABLE 1: SUMMARY OF RESVERATROL CLINICAL EFFECTS ON SEVERAL TYPES OF CANCER

S. no.	Year of the Study	Type of Cancer	Study Design	No. of Patients	Effect
1	2015	Prostate cancer	Phase 1clinical trial	14 patients	None [46]
2	2015	Prostate cancer	Randomized placebo-controlled clinical study	66 patients	None [47]
3	2017	Prostate cancer	A double-blind, randomized, placebo-controlled trial	22 men	None [48]
4	2010	Colorectal cancer	One group interventional study	20 patients	Beneficial [49]
5	2011	Colorectal cancer	Phase 1 randomized, double-blind pilot study	9 patients	Beneficial [50]
6	2012	Breast cancer	Randomized double-blinded clinical trial	39 women	Beneficial [51]
7	2014	Breast cancer	One group interventional study on postmenopausal women	NA	Beneficial [52]
8	2014	Skin cancer	One group interventional study	NA	Beneficial [53]

2.2. Resveratrol and Cardiovascular Diseases: The World Health Organization (WHO) reports that cardiovascular disease represents the main cause of death worldwide [54]. It has long been known that moderate drinking of red wine reduces the risk of heart disease [55].

The consumption of red wine provided an explanation for the 'French Paradox' that is used to describe the observation that the French enjoy the relatively low risk of cardiovascular disease despite a diet that is high in saturated fat [56]. Studies suggest that resveratrol is a main constituent in red wine, and it is suggested to play an important role in this phenomenon.

Several clinical trials have evaluated the effect of resveratrol in the management of cardiovascular diseases, one of these trials is a double-blind and placebo-controlled trial that was conducted on 40 post-infarction Caucasian patients, which were randomized into two groups.

One group received 10 mg resveratrol capsule daily for 3 months. Results of this study found that treatment with resveratrol in patients with stable coronary heart diseases improved left ventricular systolic and diastolic function. Also, the same study proved that resveratrol treatment also inhibited platelet aggregation and decreased LDL levels [57].

A randomized, double-blinded, active-controlled, parallel clinical trial was conducted on 87 subjects with stable angina pectoris. Subjects were divided into three groups: group 1 received oral supplementation with calcium fructoborate, group 2 received oral supplementation of resveratrol and group 3 received the combination of both. Treatment was continued for 60 days.

Results showed a significant decrease of high-sensitivity C-reactive protein in all groups at the 30 days and 60 days visits. The N-terminal prohormone of brain natriuretic peptide was significantly lowered for all groups; however, their combination was the most effective. Lipid markers showed slight changes from baseline in all groups. These results indicate that the resveratrol has beneficial effects in patients with angina [58].

A double-blind, randomized, placebo-controlled clinical trial comprised of 44 healthy subjects received either blend of phytochemicals (400 mg trans-resveratrol, 400 mg grape skin extract and 100 mg quercetin) or a cellulose placebo for 30 days. Results showed a decreased expression of endothelial cell ICAM, VCAM and IL-8, which may be an important mechanism contributing to resveratrol's beneficial effects on cardiovascular function [59]. A randomized placebo-controlled clinical trial performed on 18 patients investigated the effect of resveratrol on reducing diastolic blood pressure in conjunction with other phytochemicals substances (330 mg grape seed and skin, 100 mg green tea, 60 mg resveratrol, 60 mg blend of quercetin, ginkgo biloba, and bilberry). In this study, resveratrol was found to be effective in reducing diastolic blood pressure [60]. Another randomized, double-blind crossover study was conducted by Timmers *et al.,* 2011 on 11 healthy, obese men.

Subjects were divided into two groups: placebo and 150 mg/day resveratrol groups. Resveratrol was received for 30 days. Results showed that resveratrol significantly decreased intrahepatic lipid content, circulating glucose, triglycerides, alanine-aminotransferase, and inflammation markers. Also, systolic blood pressure dropped after resveratrol treatment [61]. Another prospective, open-label, randomized, controlled trial was conducted on 26 patients with type 2 diabetes mellitus in India.

Patients were randomized into control and intervention (resveratrol) groups. The results reveal that supplementation of resveratrol for 3 months significantly improves the systolic blood pressure (Mean ± SD, 139.71 ± 16.10 *vs* 127.92 ± 15.37; $P < .05$) and total cholesterol (Mean ± SD, 4.70 ± 0.90 *vs.* 4.33 ± 0.76; $P < .05$) in type 2 diabetic patients 62. **Table 2** provides a summary of these clinical trials studying the effect of resveratrol on cardiovascular diseases. Finally, resveratrol has demonstrated positive effects in studies of various cardiovascular conditions, however further research in human is necessary to verify its effectiveness.

TABLE 2: SUMMARY OF RESVERATROL CLINICAL EFFECTS ON CARDIOVASCULAR DISEASES

Study no.	Year of the Study	Type of Cardiovascular Disease	Study Design	No. of Patients	Effect
1	2016	Coronary heart disease	Randomized double-blind placebo-controlled	40 post-infarction patients	Beneficial [57]
2	2013	Angina pectoris	Randomized double-blind active-controlled	87 patients	Beneficial [58]
3	2016	Hypertension	randomized, placebo-controlled trial	18 patients	Beneficial [60]
4	2011	Hypertension and hyperlipidemia	a randomized, double-blind placebo-controlled	11 patients	Beneficial [61]
5	2012	Hypertension and hyperlipidemia	prospective, open-label, randomized placebo-controlled	26 patients	Beneficial [62]
6	2014	Atherosclerosis	a randomized, double-blind placebo-controlled	44 healthy subjects	Beneficial [59]

2.3. Resveratrol and Neurodegenerative Diseases: Neurological disorders such as Alzheimer's disease occur *via* oxidative and inflammatory damage to the central nervous system. The exact mechanism of Alzheimer's disease development is unknown. Several bio-markers have been identified which help to characterize disease onset and progression and may

serve as therapeutic targets. For instance, amyloid-β plaque accumulation caused by amyloid-beta precursor protein and increased inflammation and oxidative damage has been shown to be associated with Alzheimer's disease [63]. The potential therapeutic activity of resveratrol in Alzheimer's disease was reported by few clinical trials, which have shown that resveratrol is safe to use in patients with mild to moderate Alzheimer's disease, and it alters several Alzheimer's disease biomarkers. A randomized, placebo-controlled, double-blind, 52-week phase 2 trial of resveratrol in individuals with mild to moderate Alzheimer disease was conducted on 119 patients.

Participants were randomized to placebo or resveratrol 500 mg orally once daily. The result showed that resveratrol stabilizes the progressive decline in cerebrospinal fluid Aβ40 and plasma Aβ40 levels as dementia advances. Also, it stabilizes CSF Aβ42 levels at week 5264. Another randomized, placebo-controlled, double-blind, phase 2 trial found that treatment of mild-moderate Alzheimer's disease (AD) subjects (N = 119) for 52 weeks with resveratrol (up to 1 g by mouth twice daily) decreases levels of matrix metalloproteinase-9 (MMP-9) that degrades components of the extracellular matrix, an activity that is associated with Alzheimer's disease.

The decrease in MMP-9 may indicate that resveratrol reduces permeability and the ability of pro-inflammatory agents from reaching the brain. Furthermore, patients receiving resveratrol had a decline of cerebrospinal fluid beta-amyloid (Aβ) 42 and Aβ40 levels, indicating lower accumulation of Aβs in the brain [65].

Another 10 subjects with a mild decline in cognition were included in a double-blinded placebo-controlled pilot study. Participants were randomized into an active grape formulation arm or a placebo arm which consumed a formulation free of polyphenols for six months. The placebo arm had declines in regions of the brain known to be significantly affected in the early stages of Alzheimer's disease, while the active formulation group was spared such decline. This suggests a protective effect of resveratrol contained in grapes against early pathologic metabolic decline in Alzheimer's disease [66.]

Also, eighty post-menopausal women aged 45-85 years were randomized to take trans-resveratrol or placebo for 14 weeks to evaluate the effects on cognitive performance. These results indicate that regular consumption of a modest dose of resveratrol can enhance both cerebrovascular function and cognition in post-menopausal women, potentially offering a promising therapeutic treatment for menopause-related cognitive decline [67]. A randomized, double-blind, placebo-controlled, crossover study was conducted to evaluate the effects of oral resveratrol on cognitive performance and localized cerebral blood flow variables in 22 healthy human adults.

Resveratrol administration resulted in dose-dependent increases in cerebral blood flow during task performance, as indexed by total concentrations of hemoglobin. In contrast, the cognitive function was not affected by [68]. **Table 3** provides a summary of these clinical trials investigating the effect of resveratrol on neurodegenerative diseases.

TABLE 3: SUMMARY OF RESVERATROLS CLINICAL EFFECTS ON NEURODEGENERATIVE DISEASES

Study no.	Year of the study	Type of neurodegenerative diseases	Study Design	No. of patients	Effect
1	2015	Alzheimer's disease	Randomized, placebo-controlled, double-blind, phase 2 trial	119 patients	Beneficial [64]
2	2017	Alzheimer's disease	Randomized placebo controlled	119 patients	Beneficial [65]
3	2017	Alzheimer's disease	Double-blinded placebo controlled pilot study.	10 patients	Beneficial [66]
4	2017	cognitive decline	Randomized double-blinded placebo controlled study	80 post-menopausal women patients	Beneficial [67]
5	2010	cognitive decline	randomized, double-blind, placebo-controlled, crossover study	22 healthy subjects	Beneficial [68]

CONCLUSION: The clinical trials presented in this review have demonstrated resveratrol's therapeutic potency in the prevention and treatment of some diseases. In most of the clinical trials, the major problem was resveratrol's poor bio-availability, which is due to extensive metabolism in the liver. We found that for cardiovascular diseases and neurodegenerative disorders, the majority of clinical data showed that resveratrol had beneficial effects in patients. But resveratrol had an unclear effect on certain types of cancers. It seems that resveratrol may have specificity for certain types of cancers, so it is difficult to conclude given the small number of clinical trials that have been conducted. Overall, more clinical data are necessary in order to better understanding of resveratrol's therapeutic potential. In addition, future Pharmaceutical efforts should focus on developing a resveratrol derivative with better bioavailability.

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