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Unraveling the potentials of resveratrol: An important polyphenolic compound in health with clinical significance in chronic diseases

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Abstract
A stilbenoid, natural phenol, called resveratrol (3, 5, 4′-trihydroxy-trans-stilbene), is a phytoalexin produced by a number of plants in reaction to injury by pathogens like bacteria or fungi. As a member of the viniferin family of polyphenols, resveratrol is one of the most well-known and extensively researched substances. Free radical-induced oxidative stress is a key component in the pathogenesis of atherosclerosis, neoplasia, and neurological disorders. Consequently, much attention has been given to the naturally occurring phytochemical antioxidants as a possible treatment. Resveratrol has shown potential in enhancing treatment for diabetes, obesity, colorectal cancer, breast cancer, Alzheimer's disease, stroke, metabolic syndrome, hypertension, multiple myeloma, kidney disease, inflammatory disorders, and metabolic syndrome. It acts as a pharmacological preconditioning substance, boosting the effectiveness of alternative medicine. Resveratrol also strengthens the immune system's defense against cancer by modulating immune cell responses within tumors. This review presents evidence supporting the preventive use of resveratrol for various chronic ailments.

Keywords: Resveratrol, anti-inflammatory, neuroprotective, metabolic diseases, immunomodulator

Introduction

Resveratrol, a natural polyphenolic compound devoid of flavonoids, is present in a variety of fruits and vegetables including grapes, cacao, peanuts, and peanut sprouts. It was initially isolated from the roots of white hellebore in 1939. The French paradox, characterized by the relatively low occurrence of obesity and cardiovascular disorders among the French population despite a high-fat diet, is often attributed to the consumption of red wine, which is rich in resveratrol [1]. Since 1997, there has been notable advancement in scientific research pertaining to resveratrol. A study conducted during that period demonstrated its potential in impeding carcinogenesis in mice [2]. In recent times, resveratrol has garnered substantial interest from dieticians, nutritionists, medicinal chemists, and health professionals owing to its multifaceted advantages, encompassing anti-aging properties, anti-inflammatory effects, antidiabetic effects, and the prevention of cardiovascular diseases. Resveratrol has also exhibited efficacy in targeting diverse biological pathways, notably inflammation, oxidative stress (characterized by augmented production of free radicals or diminished synthesis of antioxidant molecules), apoptosis, mitochondrial dysfunction, and angiogenesis [3]. Furthermore, via redox, inflammatory, and immune signalling pathways, as well as interactions with glucose and lipid metabolism, multiple experimental studies have substantiated the therapeutic potential of resveratrol in diverse disease conditions, encompassing cardiovascular diseases (CVDs), diabetes, obesity, liver diseases, Alzheimer's disease, and Parkinson's disease [4]. The neuroprotective effects of red wine involved in several bioactive molecules, including quercetin, myricetin, catechins, tannins, anthocyanidins, ferulic acid, and resveratrol is evident through certain studies [5]. Numerous studies have also demonstrated that resveratrol provides a wide range of therapeutic and preventative options against numerous diseases, including various cancers [6]. Moreover, research on acquired and hereditary models of iron overload has demonstrated that resveratrol mediates therapeutic hepatic effects [7]. Resveratrol does not appear to enhance lifespan in healthy mice or in a model of premature ageing, according to recent evidence, but it does appear to postpone or attenuate several age-related changes and prevent early mortality in obese animals [2]. Certain studies conducted *in vitro* and *in vivo* characterization of RSV, found that it is absorbed in larger quantities by enterocytes after oral administration. Absorption from ingested food has limitations resulting in only small portion of RSV reaching bloodstream and body tissues. Bioavailability of trans-resveratrol through oral route is 12% [4].

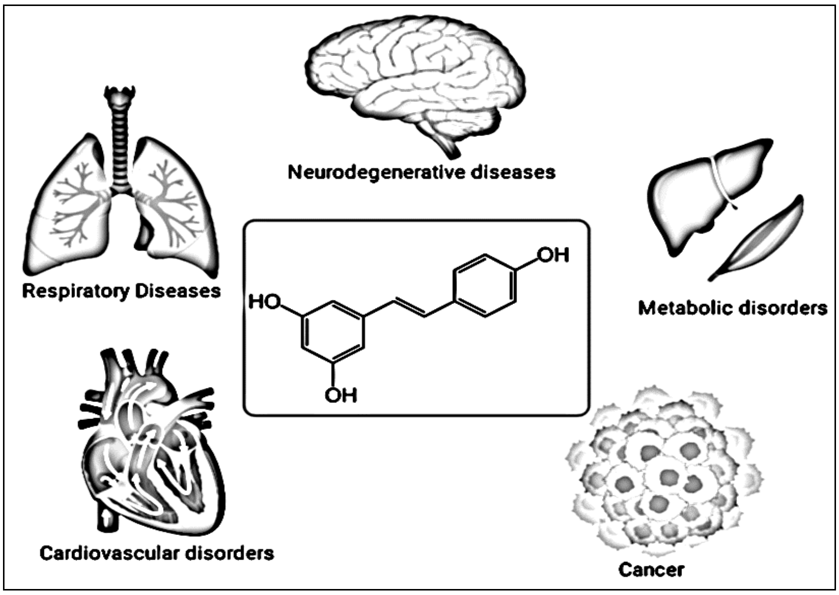

Fig 1: Resveratrol in various health diseases

There are numerous ways in which resveratrol exerts its therapeutic effects. Resveratrol interacts with several receptors, kinases, and other enzymes that may very well play a significant role in its biological effects. Adenosine monophosphate-activated protein kinase (AMPK) and Sirtuin 1 (SIRT1), both of which affect the regulation of metabolism in several tissues, are stimulated by resveratrol administration *in vivo* [2].

Materials and Methods

A literature search was conducted using keywords 'resveratrol and obesity', 'resveratrol and health', 'resveratrol and cardiovascular diseases', 'resveratrol and metabolic effects', 'resveratrol and diabetes', 'resveratrol and anticancer effects'. A search was conducted on CTRI website for clinical trials on resveratrol using keyword 'resveratrol' and another search for patents was conducted on Espacenet.

Results and Discussion

Obesity: The disease of obesity is common and is accompanied by several, major comorbidities. These include cancer, obstructive sleep apnea syndrome, metabolic syndrome, diabetes mellitus, cardiovascular disease, hypertension, and sexual and hormonal abnormalities [1]. The surge in obesity predominantly arises from lifestyle alterations, characterized by excessive food intake and reduced physical activity. Prolonged periods of energy intake surpassing energy expenditure leads to the development of an obese phenotype. Elevated body mass index (BMI) serves as a risk factor for various conditions, including type 2 diabetes, cardiovascular disease, dyslipidemias, non-alcoholic fatty liver disease, gallstones, Alzheimer's disease, and certain malignancies. Obesity exerts significant detrimental effects on health. Controlling obesity involves strategies such as reducing energy consumption, increasing energy expenditure, or a combination of both. This can be achieved by modifying dietary habits, engaging in regular physical activity, and enhancing overall energy expenditure. While these approaches are effective for most individuals, some may require alternative interventions such as surgical procedures or drug therapies [8]. Resveratrol (RSV), for instance, enhances exercise endurance by significantly boosting the aerobic capacity and oxygen consumption of the gastrocnemius muscle in mice. RSV therapy achieves this by activating the peroxisome proliferator-activated receptor coactivator (PGC1) via the nicotinamide dinucleotide (NAD) dependent deacetylase sirtuin-1 (SIRT1), resulting in improved oxidative phosphorylation and mitochondrial biogenesis, ultimately enhancing insulin sensitivity [9]. Numerous researchers have found out potential benefits of RSV to treat metabolic diseases during the last decade. But the results obtained from animal models through the trial conducted on obesity have shown resveratrol's inability in reduction of obesity. Yet it is being studied widely in the field of obesity [8].

Table 1: Studies conducted on resveratrol in different models for obesity

Study model	Description	Findings	References
Mice	High Fat Diet (HFD)induced mice were assessed by interaction between gut microbiota & resveratrol	• Reversal in weight gained • Improvement in composition of gut microbiota & intestinal permeability • Enhancement in metabolic phenotype • Alteration in makeup & functionality of gut microbiota	[10]
Mice	Resveratrol ingestion (0.4% of the diet) over six months in HFD-mice	Significant increase in survival & insulin sensitivity without reducing body weight.	[11]
3T3-L1 preadipocytes	Resveratrol concentrations 10,20,40 & 80 µM was used for cell incubation for 48 hrs Study on gene & protein PPARγ, C/EPBα & SREBP-1C with concentrations 10,20,40 & 80 µM	Concentrations 20-80 µM reduced lipid accumulation Concentrations 20-80 µM reduce both gene & protein expression Overall, Resveratrol reduces adipogenesis	[8]
Early weaning rats	Resveratrol administration of dose 30mg/kg/body weight during 30 days	Prevention of higher body weight, visceral obesity, hyperleptinemia, central leptin resistance, hyperglycemia as well as hypoadiponectineia.	[12]

Diabetes: Diabetes is fast growing global non-communicable epidemic disease in which 360 million people are likely to suffer from this metabolic disorder in the year 2030 [13]. Many studies have suggested that resveratrol is blood sugar lowering ingredient for type 1 and type 2 diabetes. Basically antidiabetic effect involves lowering of glucose in blood, improvement in sensitivity towards insulin and by preserving the pancreatic β-cells. Resveratrol is also found to alleviate blood sugar complications [13]. Insulin acts on the endothelium to attract unperfused capillaries and enhance blood flow, which can affect the rate of glucose uptake in skeletal muscle and adipose tissue [14]. Deficiency to secrete insulin in the required amount also results in disturbances in the biochemical mechanisms of the bodily functions, which in turn leads to hyperlipidaemia as well as cardiac and kidney failure [15]. Reduced insulin-mediated glucose uptake in skeletal muscle, the liver, and adipose tissue in patients with normal glucose tolerance is the major anomaly of and risk factor for T2DM [14].

Table 2: Effects of Resveratrol in diabetes

Study Model	Description	Findings	References
Type 2 Diabetes Individuals and Animal models	Resveratrol administration 2.5-400mg/kg for 1-6 months	• Increase insulin sensitivity • Reduce circulating insulin concentration	[13]
Diabetic Patients	12 months of resveratrol administration	• Reduces diabetes • Ameliorates insulin reactivity	[13]
Insulin resistant rats on high cholesterol-fructose diet	Promoting GLUT4 translocation to cell membrane & insulin receptor phosphorylation in soleus muscles	Improves whole-body and tissue-specific insulin-stimulated glucose uptake	[14]
Sprague-Dawley rats	The rats were induced with diabetes by streptozocin 50mg/kg and treated with resveratrol	▪ The elevation in serum blood glucose levels, insulin levels and dyslipidemia were significantly improved ▪ Resveratrol ameliorates hyperglycemia & serum glucose dysfunction	[15]
Type 1 diabetic individuals	Exploratory trial conducted on 13 patients by administration of resveratrol for 60 days in line	▪ Strong antidiabetic effect	[16]
Rhesus monkey	Daily administration of resveratrol for 2 years with 80 mg/day for first year and 450 mg/day for the second year in diet induced obesity	Increase in insulin sensitivity	[17]

Some clinical investigations have contradicted a meta-analysis that claimed there were no substantial antidiabetic advantages of resveratrol for persons without type 2 diabetes [14]. A study found that treatment with 0-10 µM trans-resveratrol for nine days inhibited IL6, IL8, and VEGF expressions in the human retinal pigment epithelial cells (ARPE-19), indicating that resveratrol protects the retinal cells from inflammation and gap junction intracellular communication (GJIC) degradation caused by hyperglycemia [18].

Cardiovascular diseases (CVS): Resveratrol shows major contribution in different issues related with cardiovascular system which appears to be directed towards limiting the progression of heart disease.

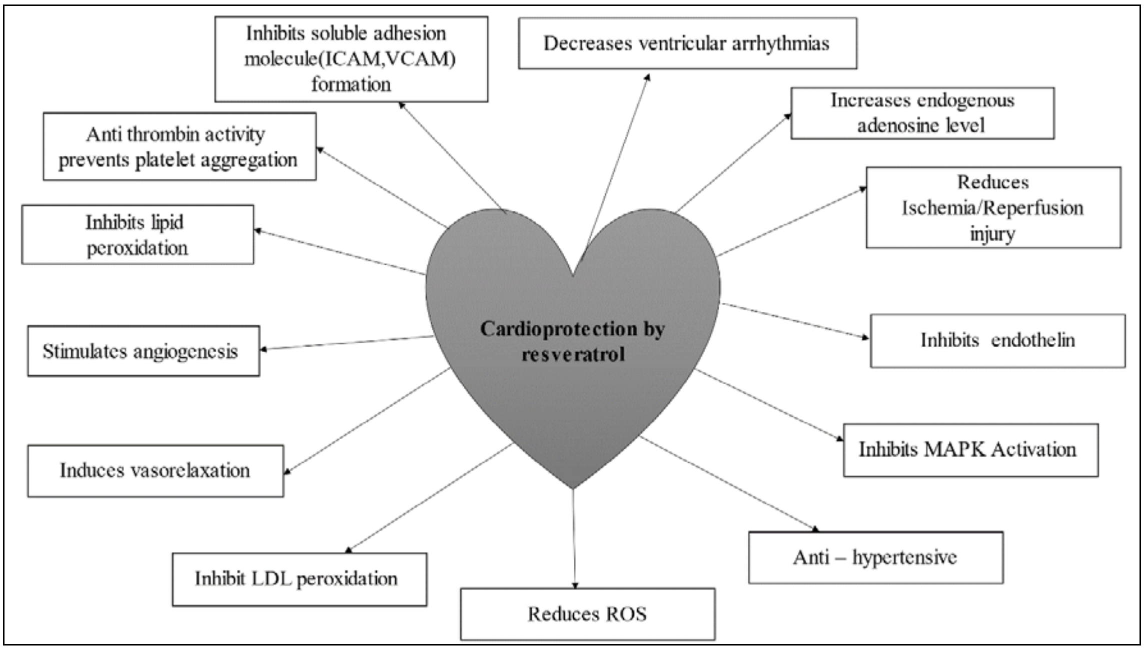

Fig 2: Cardio protective role of resveratrol

The incidence of cardiovascular diseases (CVDs) and associated ailments is witnessing an upward trend, prompting scientific investigations into preventive strategies targeting these interconnected conditions. Recent epidemiological findings substantiate that early exposures to environmental factors escalate the likelihood of developing adult CVD and kidney diseases [19]. Resveratrol, a bioactive compound, exhibits pleiotropic effects on various organ systems. Both animal and human trials have investigated the utilization of resveratrol as a nutraceutical for multiple disorders [20]. Resveratrol has demonstrated beneficial effects in animal models of various cardiovascular diseases (CVDs), such as atrial fibrillation, heart failure, myocardial ischemia-reperfusion injury, vascular disease, hypertension, endothelial dysfunction, cardiomyopathy, atherosclerosis, and stroke. A study involving 1000 participants found that higher levels of the urine resveratrol metabolite were associated with a reduced risk of cardiovascular events. In animal models, resveratrol has also shown positive effects against kidney diseases, including the reduction of inflammation, oxidative stress, and tubulointerstitial damage. Additionally, it has been found to enhance antioxidant activity, decrease mesangial cell proliferation, reduce glomeruli matrix expansion, and improve renal function [20].

Due to its wide range of effects, resveratrol is considered a promising molecule for managing the risk factors, development, and progression of atherosclerosis. Several studies have demonstrated that resveratrol can reduce various risk factors associated with atherosclerosis, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), apolipoprotein B (Apo B), lipoprotein A (Apo A), free fatty acids (FFA), and triglycerides (TG). Additionally, resveratrol has been shown to improve the levels of high-density lipoprotein cholesterol (HDL-C), also known as "good cholesterol," in humans. Resveratrol has also been found to prevent the elevation of TC, TG, LDL-C, and HDL-C levels, as well as reduce atherosclerotic lesions induced by a high-fat diet and lipopolysaccharide, providing further evidence of its potential in lowering lipids and combating atherosclerosis [21].

Alzheimer's and Parkinsonism: Dementia is a type of Alzheimer's disease (AD) and is continuously increasing day by day. In this disease, patient's memory decreases gradually and their cognitive function is affected [22]. Resveratrol is considered as prophylaxis in neurodegenerative diseases i.e., AD, Parkinson disease, amyotrophic lateral sclerosis in which higher oxidative damage is observed because of antioxidant & anti-inflammatory properties [23]. Water maze experiment conducted on mice demonstrated RSV could enhance the learning ability of mice model [22]. Several studies have reported that resveratrol (RSV) can improve learning and memory in patients with Alzheimer's disease (AD). One of the primary neuroprotective mechanisms of resveratrol is the activation of SIRT1, a protein expressed in the adult human brain, predominantly in neurons. Resveratrol stimulates the activation of SIRT1, which in turn inhibits microglial cell death induced by beta-amyloid and enhances cognitive performance. These findings suggest that resveratrol has potential as a therapeutic agent for AD by promoting SIRT1-mediated neuroprotection and cognitive improvement [23]. Researchers investigating the effects of resveratrol (RSV) on a mouse model of Alzheimer's disease (AD) observed that RSV-treated mice exhibited elevated levels of nuclear Nrf2 and enhanced translocation of Nrf2. Moreover, these mice demonstrated increased expression of heme oxygenase-1 (HO-1). These findings suggest that RSV may improve spatial memory in experimental mice by upregulating the expression and activity of key antioxidant enzymes, such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). These enzymes play vital roles in mitigating oxidative stress, which is a central feature of AD pathology [24].

Parkinson's disease (PD), a degenerative neurological ailment that affects 1% of people over 65 worldwide, is characterized by bradykinesia, stiffness, tremor, and postural instability [25]. Drug's effectiveness in PD can be evaluated by behavioral analysis of motor function. A review was conducted, in which 4 research studies were involved. It revealed that RSV showed ameliorating motor functions in behavioral experiments. A meta-analysis performed on the outcome of TH^+ neuron counts in PD models by a method – forest blot. The outcome demonstrated that the amount of TH+ neurons was significantly elevated in the resveratrol-administered group when it was in contrast when comparing the group of MPTP-induced PD mice given vehicle treatment [26]. Few scientists evaluated the potential effects of RSV in rats given rotenone injections. They noticed that RSV reduced ER stress, which was followed by a drop in ER stress markers such C/EBP homologous protein (CHOP) and glucose-regulated protein 78 (GRP78) in the brain, which inhibited caspase-3 activation. RSV also altered the equilibrium between the oxidant-antioxidant systems in this PD rat model by activating the Nrf2 signaling pathway [24].

Anti-inflammatory Effect: Resveratrol therapy has been demonstrated to provide vaso-protection in aging mice and rats. This protective effect is attributed to several mechanisms, including the reduction of reactive oxygen species (ROS) production, enhancement of endothelial function, inhibition of inflammatory processes, and attenuation of endothelial cell death. These beneficial effects contribute to the preservation of vascular health and function in aging animals [27]**.** The antioxidant properties of resveratrol are well-supported by numerous *in vitro* studies. Resveratrol has been found to inhibit the formation of oxygen free radicals through the suppression of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, consequently reducing the generation of reactive oxygen species. Additionally, resveratrol promotes the production of antioxidant enzymes and their respective substrates, leading to a reduction in overall oxidative stress. Furthermore, resveratrol's vasoprotective effects are mediated by an upregulation of endothelial nitric oxide synthase (eNOS), which subsequently enhances the generation of nitric oxide (NO) by endothelial cells. This increase in NO production contributes to the vasoprotective actions of resveratrol [28].

The anti -inflammatory properties of resveratrol are similar to the mechanisms of aspirin by targeting cyclooxygenase -1 (COX -1) and cyclooxygenase - 2 (COX -2) and inhibiting prostaglandin activity [28]. Other research demonstrated that sirtuin-1 (SIRT-1), one of the anti-inflammatory pathways activated by resveratrol, is one of the substance's positive benefits [28]. RSV has been shown to have anti-inflammatory effects in cardiac tissue, which were supported by the suppression of IL-1, iNOS, and ICAM-1 messenger RNA (mRNA) expression in human coronary artery endothelial cells stimulated by TNF- and treated with RSV. RSV has already been shown to suppress TNF- and IL-6-induced increases in monocyte adhesion in primary human coronary artery endothelial cells, which lowers pro-inflammatory NF-B levels. Another study found that when TNF- or IL-13 are used to activate human pulmonary artery endothelial cells, RSV lowers the amount of eotaxin-1, a chemokine linked to eosinophil recruitment. The expression of the pro-inflammatory transcription factors Janus kinase 1 (JAK1), phosphorylated extracellular signal-regulated kinase (ERK) 1/2, c-Jun N-terminal kinase (JNK), and signal transducer and activator of transcription (STAT) 6 was then inhibited. Finally, the p65 subunit of NF-B was decreased [29]. Additionally an investigation showed that, in the acute pharyngitis model, the vocal cord index and absorption index were higher than in the control group. When compared to the acute pharyngitis model group, resveratrol therapy significantly decreased the index of the vocal cords and absorption index in acute pharyngitis rabbits [11].

Immunomodulatory and Anti-Cancer effect

Immunomodulation of the tumor microenvironment is a vital area of research in cancer treatment. The tumor microenvironment comprises various non-tumor cells, predominantly endothelial cells, cancer-associated fibroblasts, and immune cells. The immune cell populations present in the tumor microenvironment encompass myeloid-derived suppressor cells, tumor-associated macrophages, cytotoxic T cells, natural killer cells, B cells, CD4+CD25+FOXP3+ regulatory T cells, and tumor-associated macrophages. Understanding the interactions and functions of these diverse immune cells within the tumor microenvironment is crucial for developing effective immunotherapies for cancer patients [30]. The immune cells mentioned earlier play significant roles in the pathogenesis of tumor growth and development. It is worth noting that resveratrol, in combination with other natural substances, has been investigated in various studies for its potential to inhibit tumor cell proliferation and metastasis by activating the immune system. Recent research suggests that resveratrol acts as an immunomodulatory agent that can stimulate immune cells within the tumor microenvironment. Additionally, resveratrol may render cancer cells more vulnerable to cytotoxic signals from immune cells, enhancing their ability to target and eliminate cancerous cells. These findings highlight the potential of resveratrol as an immunomodulatory drug for cancer therapy [31].

According to a recent study conducted by a scientist, resveratrol has been found to target PD-L1, a molecule involved in immune suppression, in order to enhance anti-tumor T-cell immunity. The study utilized the JIMT-1 cell line, which represents an aggressive subtype of basal-like/HER2-positive breast cancer known for its natural overexpression of PD-L1. Resveratrol treatment was found to significantly enhance the immune surveillance of cytotoxic T-lymphocytes against breast carcinoma cells, indicating its potential to boost the immune response against cancer cells by modulating PD-L1 [30]. According to another recent study, resveratrol was found to inhibit the expression of immune-checkpoint and proliferative genes induced by thyroid hormone in oral cancer cells. The researchers observed that thyroxine, a thyroid hormone, increased the expression of proliferative genes in human oral cancer SCC-25 and OEC-M1 cells, as well as immune-checkpoint genes such as PD-L1 and BTLA (B- and T-lymphocyte attenuator). However, resveratrol treatment prevented the upregulation of PD-L1 and BTLA gene expression. This research suggests that resveratrol has the potential to counteract the immune-checkpoint gene expression induced by thyroid hormone, thus protecting cancer cells from immune surveillance [30].

Apoptosis has also been demonstrated to be induced by resveratrol in a number of cancer cells through regulation of the mitogen-activated protein kinase (MAPK) pathway and suppression of the PI3K/AKT/mTOR pathway. According to reports, resveratrol's anti-tumor activities necessitate MAPK-induced P53 activation and apoptotic induction. Additionally, it has been demonstrated that resveratrol causes apoptosis in breast, prostate, ovarian, uterine, and myeloma cells [30]. Resveratrol, when used as an adjuvant therapy, has shown the ability to suppress the upregulation of NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) in cancer cells, leading to their death. This suppression of NF-kB by resveratrol may also contribute to the reduction of immunological checkpoint upregulation. The effects of resveratrol are particularly interesting when used in conjunction with other tumor therapy techniques. Resveratrol can contribute to cancer prevention through various mechanisms, including the control of intercellular cytokines and growth factors, as well as the induction of apoptosis in cancer cells. Its multifaceted effects make it a promising compound in the fight against cancer [32].

Clinical Trials on resveratrol for the treatment of COPD [33]

There have been overall 199 clinical trials conducted/being conducted on resveratrol out of which 71 studies are being conducted in United States, where India has not reported single study being conducted on Resveratrol so far.

Patents on Resveratrol: Patents were searched on the database of Espacenet and the number of patents from various countries were calculated in percentage and depicted in Fig 3.

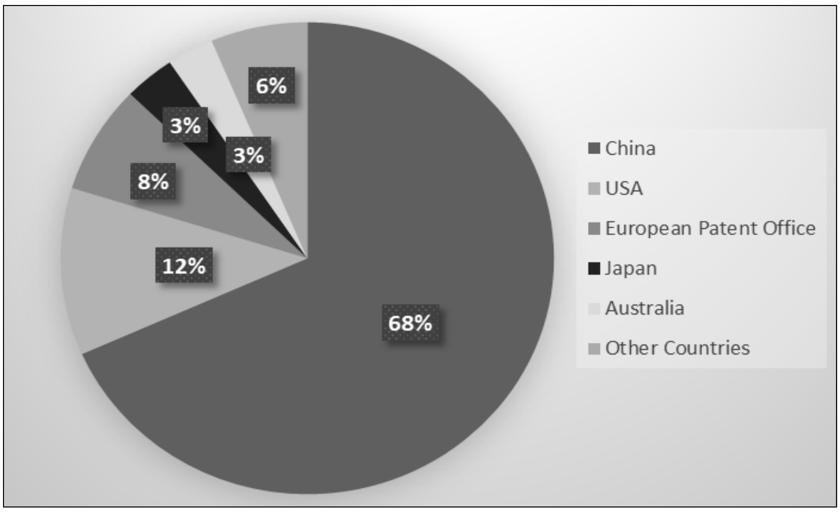

Fig 3: The figure shows the percentage of patents from various countries on Espacenet [34-39]

Resveratrol Market Highlights: [40]

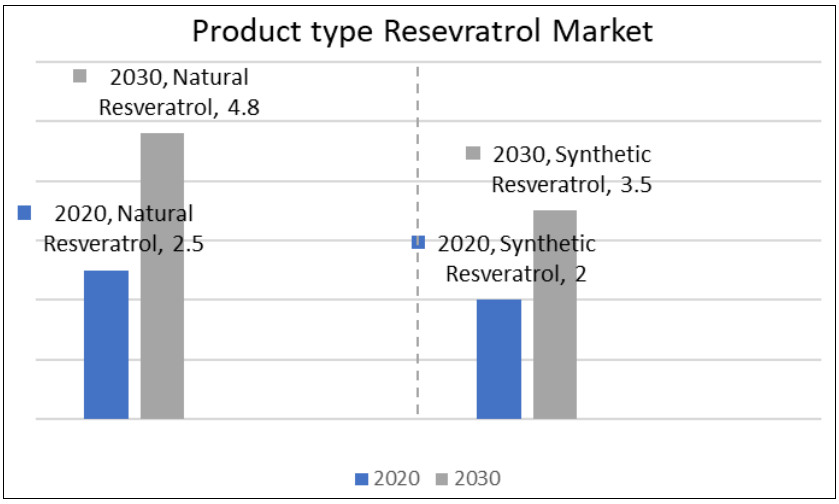

Fig 4: Resveratrol Market by Product type

Table 4: Resveratrol Market Report Highlights

Aspects	Details
Product type	Natural Resveratrol, Synthetic Resveratrol
Form	Powder, Liquid
Application	Dietary Supplements, Pharmaceuticals, Cosmetics, Others
Region	North America, Europe, Asia-Pacific, LAMEA (Brazil, Saudi Arabia, South Africa, Argentina, Rest of LAMEA)
Key Market Players	Botaniex inc., chongqing kerui nanhai pharmaceutical co., ltd., evolva, foodchem international corporation, good-yg-biotech, haihang industry co., ltd, hubei sanxin biotechnology co., limited, honghao herb, sichuan xieli pharmaceutical co. Ltd, xi'an chen lang biological technology co., ltd

Discussion

Resveratrol, a natural polyphenolic compound found in various plant sources like grapes, berries, and peanuts, has indeed attracted significant interest for its potential preventive and therapeutic effects against various disorders. Extensive preclinical research has demonstrated a wide range of effects associated with resveratrol, making it a subject of considerable scientific investigation. Studies have shown that resveratrol can improve insulin sensitivity, regulate blood glucose levels, and mitigate complications associated with diabetes. Additionally, resveratrol's immunomodulatory properties have been explored, suggesting its potential in modulating immune responses and supporting overall immune system function. Resveratrol has also been investigated for its potential anti-cancer effects. Numerous preclinical studies have demonstrated its ability to inhibit the growth of cancer cells, induce apoptosis (cell death) in cancer cells, and prevent the formation of blood vessels that supply tumors. However, it's important to note that while promising, the translation of these findings to effective cancer treatments in humans is still being explored through clinical trials. Furthermore, resveratrol exhibits anti-inflammatory properties, which can help reduce inflammation in the body. Resveratrol's anti-inflammatory effects make it an interesting target for further research in these areas.

Conclusion

The use of resveratrol in clinical trials and as a treatment option is expanding. Clinical studies have investigated its potential therapeutic applications in various conditions, including cardiovascular diseases, cancer, neurodegenerative disorders, and metabolic disorders. While there is a need to develop more data on safety and efficacy of resveratrol in humans at various doses. Additionally, the mention of China as the country with the highest number of patents on resveratrol indicates the significant research and commercial interest in this compound. However, it's essential to note that while resveratrol shows promise, consultation with healthcare professionals and relying on evidence-based information is crucial when considering the use of resveratrol or any other natural compounds for prevention or treatment of specific disorders.

Declaration of Interest

The authors state no conflict of interest.

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