Review Article

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Resveratrol: a polyphenol with multiple health benefits

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Abstract:

In today's stressful world, there is an urgent need for simple drugs to combat lifestyle diseases like heart diseases and diabetes, which are assuming epidemic proportions. Resveratrol is one such molecule. It is the molecule behind a phenomenon known as the "French paradox", i.e. the observation of low incidence of heart disease in France in spite of a diet rich in fats. It is a major component of red wine, also part of the French diet. Resveratrol is a naturally occurring polyphenolic phytoalexin, derived from the skin of plants, which has gained interest exponentially in recent years. This molecule is found to have a number of health benefits, including prevention of cardiovascular and neurodegenerative diseases. It is known to have anti-inflammatory, antiviral, anti-platelet aggregation and many other health beneficial properties. It has found tremendous clinical application. Among its wide range of biological activities, the most striking activity is of cancer and tumor initiation prevention. This molecule has been shown to have a positive effect on metabolism and improvement in overall health of an individual and can probably be used as an anti ageing drug alone or in combination with some other medication. These remarkable properties have elicited a huge interest of researchers in this molecule. It has been reported to interfere with some major cellular signaling pathways which are involved in cell survival or cell death. Careful insights into these cellular pathways and their interaction with resveratrol could pave the way for future drug designing for treatment of diseases. Here we have tried to review the maximum possible biological properties of resveratrol cited so far in the literature.

Keywords: Resveratrol, Calorie restriction, antioxidants, neurodegenerative disease, diabetes, Sirtuins

Introduction

Dietary polyphenols have gained considerable importance over the past 10 years due to the plethora of health benefits they provide. They play a major role in prevention of many cardiovascular and neurodegenerative diseases **[1, 2]**. They help fight oxidative stress with their antioxidant properties. There exist a large variety of polyphenols differing greatly in their biological activities. Some polyphenols are products of plants produced as a result of their defense action against infection, stress or injury. Flavonoids are one of the major classes of polyphenols which have antioxidant properties. They scavenge free radicals in the body and protect against oxidative stress **[3]**. They improve cell survival and are beneficial for improving the overall health of the individual. Polyphenols are known to improve endothelial function, inhibit platelet aggregation, fight inflammation and many more health benefits. They have immense potential to promote vitality and maintain good health. Thus now it is very much evident that fruits and vegetables are essential, not just for vitamins and minerals, but for their polyphenol content also. This review performs a brief survey about one such particularly naturally occurring polyphenol, resveratrol, which is produced by several plants when under virus attack or in response to external stimuli in their defense. Like other polyphenols, it also has several health benefits, which we will try to discuss in detail. It has both potential therapy and prevention ability towards diseases **[4]**.

2.Resveratrol

Resveratrol (3,4',5-trihydroxystilbene) is a naturally occurring polyphenolic phytoalexin (antibiotic) that is found in a large amount of plant species (at least 72), a number of which are components of the human diet, including grapes (Vitis vinifera), plums, mulberries and peanuts. It is produced by these plants in response to stress, injury, ultraviolet irradiation and fungal (Botrytis cinerea) infection as part of their defense mechanism. It is much better adsorbed than other polyphenols when orally administered **[4, 5]**. It is a major constituent of red wine, which contains 6.5 mg L^{-1} resveratrol **[6, 7, 8]**. At present, it is difficult to calculate the amount of resveratrol which can be distributed to the organs and tissues of an animal after digestion. It is a fat soluble antioxidant which protects the cell membranes, its solubility in water being 0.03g L^{-1}, while that in DMSO is 16g L^{-1}. Resveratrol is undoubtedly the most notable polyphenol since 1993 when Frankel et al. **[9]** discussed its inhibitory effects against oxidation of low density lipoproteins (atherosclerosis) and in prevention of heart attacks. Epidemiological studies have shown an inverse correlation between red wine consumption and incidence of cardiovascular diseases (also called the "French paradox") which raised further interest in this compound.

2.1 Sources of Resveratrol

Resveratrol was first isolated from the roots of white hellebore in 1940 and later, in 1963, from the roots of Polygonum cuspidatum used in both Chinese and Japanese medicines. It was initially characterized as a phytoalexin but gained considerable attention when it was postulated to explain some of the cardioprotective effects of red wine **[9]**. Red wine is the most common source of resveratrol, with concentrations of up to 14 mg L^{-1}, but its concentration varies between and within each type of grapes used. White wines generally have concentrations less than 0.1 mg L^{-1}**[10, 12]**. Resveratrol is also reported to be present in peanuts, soys and other plant products although the amount is almost negligible compared to that in wines **[10, 11]**. A number of resveratrol supplements have been developed, with capsules containing anywhere from 1 mg through to as much as 1g per dose. Recently trans resveratrol has also been found in dark chocolate **[13]**.

2.2 Isomers or diastereomers

Resveratrol exists in both cis and trans isomeric forms, the major form being the trans isomer, which contributes most to its biological activities and health benefits [12]. The trans isomer can isomerize to the cis form on UV exposure **[14].** Recently, it has been found that when cis resveratrol is exposed to UV radiation, it forms a new highly fluorescent compound, resveratrone **[15]**. In plants, it mostly exists in glycosylated piceid forms (3-O-β-D-glucosides). The trans isomer of resveratrol displays a number of pharmacological effects in vitro, ex vivo, and/or in vivo, but much less is known about the pharmacological activity of the cis isomer, possibly as a result of its low commercial availability. Trans-resveratrol has been found to have more therapeutic potential as compared to cis-resveratrol **[16]**.

It has been proved in multiple animal studies and human trials that the predominant compound that is orally ingested with foods is trans-resveratrol glucoside (piceid), which is less biologically active due to its esterified hydroxyl groups, and is rapidly eliminated from the body **[5]**.

2.3 Metabolites of resveratrol

Several metabolites of resveratrol have been identified in human plasma or urine. Glucuronides and sulfates are the most frequently found metabolites of resveratrol **[17]**. Despite its efficient absorption after oral administration, resveratrol's hydroxyl groups rapidly metabolize as sulfate and glucuronide in vivo, and this is the reason for its low bioavailability in spite of high oral dose **[18]**. It is metabolized in the liver and excreted by the kidneys. Additionally, it is important to note that resveratrol is transported to tissues by plasma proteins, with albumin being a major transporter. Hence there is need to develop resveratrol derivatives which have high bioavailability compared to resveratrol, but having the same beneficial effects. Various experimental studies were conducted to assess the metabolites of resveratrol **[19, 20]**. Boocock and co-workers **[20]** reported that after oral intake of 1 g resveratrol, two monosulfate conjugates, one disulfate, two monoglucuronides, and one glucuronide–sulfate were detected. The nature and quantity of metabolites differed between different subjects, which indicates its high variability **[21]**. Sulfate metabolites were less frequently found when compared to glucuronide metabolites due to its poor chromatic behavior **[18]**. However, when resveratrol was administered in high dose, sulfates were the main metabolites **[22]**.

2.4 French paradox

A primary impetus for research on resveratrol was initiated from the paradoxical observation that moderate consumption of red wine leads to low incidence of cardiovascular diseases in spite of a high-fat diet intake by the people in France, a phenomenon known as the French paradox **[23, 24]**. The resveratrol in red wine is believed to be the reason behind this phenomenon, because of its ability to inhibit lipid peroxidation and prevent cholesterol formation **[6, 23]**. The French paradox may be regarded as a good generalization of the effects of long term red wine consumption on cardiovascular health. The possible action mechanisms of resveratrol may involve inhibition of platelet

aggregation, arterial vasodilation, favorable changes in lipid metabolism, antioxidant effects, stimulation of angiogenesis, induction of cardioprotective protein expression, and insulin sensitization **[5]**. In fact, it reduces the synthesis of certain lipids and eicosanoids that tend to promote inflammation and atherosclerosis **[25]**.

Difference between flavonoids and resveratrol

Flavonoids are the polyphenol class of compounds mostly concentrated in the skin of plants and are often associated with protection from environmental stress, such as ultraviolet radiation. Flavonoids are renowned for their antioxidant action. They are the most important plant pigments responsible for the color of plants. Like flavonoids, resveratrol is also a polyphenol, but despite this similarity, their biological properties differ considerably.

The structural difference between the two could justify the variation in their properties. The presence of a p-hydroxyl group in ring A and the conjugated double bond (Fig. 1) is considered essential for effective radical scavenging by resveratrol **[26]**. The presence of a double bond between the two rings A and B makes the electrons more delocalized and gives rise to the quinine structure, which is highly resonance stabilized, while the p-hydroxy group possesses electron donating properties and is a radical target. The flavonoid structure is altogether different when compared with resveratrol with a phenyl pyrone backbone and no stilbene like structure. The general structure for both is shown in Figure 1 below.

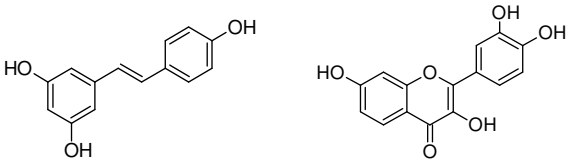

Fig. 1 Structure of trans-resveratrol and the general structure of flavonoids

Khanduja and Bhardwaj **[27]** compared the antiradical activity of resveratrol with various other bio-flavonoids but found no direct relationship between the two. There was no clear demarcation of why some flavonoids are better radical scavengers and why some show poor activity when compared with resveratrol.

3.Health Benefits

Resveratrol has been shown to have a number of health benefits, including anticarcinogenic **[28]**, anti-inflammatory **[4]** and anti-estrogenic activities **[29]** as well as cardiovascular protection **[30]**, free-radical Scavenging **[6, 31],** inhibition of platelet aggregation **[32],** antihyperglycemic or antidiabetic **[33, 34]** and neuroprotection **[35].** It has also been shown to alter protein catabolism and functions and to provide resistance against oxidative stress, injury, and cell death caused by ionizing radiation. The list goes on. In fact, a current topic of research is how such a small simple molecule can have so many health benefits. Apart from its various above mentioned health benefits, its most noticeable and striking feature is of promoting longevity, i.e. it delays ageing by increasing the lifespan of human cells. The exact mechanism of action and the protein involved is discussed in a separate section.

3.1 Resveratrol as an antioxidant

Multiple studies have shown resveratrol to be a potent free radical scavenger both in vitro and in vivo. Resveratrol's activity as an antioxidant refers to its ability to transfer a hydrogen atom or an electron. Hussein **[26]** in 2011 evaluated resveratrol for possible antioxidant activity, namely reducing power, chelating activity with Fe^{2+}, free radical scavenging, total antioxidant, superoxide radical scavenging, hydrogen peroxide scavenging, hydroxyl radical scavenging activity and free radical scavenging activity, and compared this with the activites of natural and synthetic antioxidants, such as tocopherol, ascorbic acid, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA) and trolox. The antioxidant activity of resveratrol was found to increase with increasing concentration. His study showed that resveratrol exhibits quite a high antioxidant activity, and could be considered as a source of natural antioxidants. Leonard et al. **[36]** in his studies measured the effect of resveratrol on several different systems involving the hydroxyl, superoxide, metal/enzymatic-induced, and cellular generated radicals. It was found to be an effective scavenger of hydroxyl, superoxide, and metal-induced radicals. Resveratrol also exhibits a protective effect against lipid peroxidation in cell membranes and DNA damage caused by reactive oxygen species (ROS) **[37].** Frankel & co-workers **[9]** were the first to demonstrate that trans-resveratrol inhibited LDL oxidation by cupric ion. Cupric ions behave as pro-oxidants and release free radicals from lipid molecules (PUFA). Resveratrol chelates these copper ions and hence inhibits LDL peroxidation.

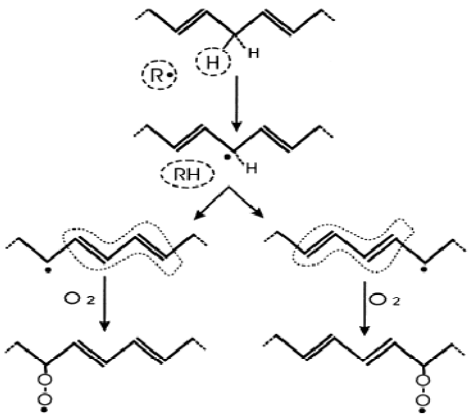

Fig.2 Mechanism of lipid peroxidation **[48]**

It also prevents lipid peroxidation in PC12 cells induced by iron and ethanol **[38].** It decreases LDL cholesterol oxidation, and therefore the pro-inflammatory cascade that ultimately leads to atherosclerotic plaques **[39, 40].** It also scavenges the RNS/ROS peroxynitrite. Holthoff et al. **[41]** demonstrated the mechanism of the peroxynitrite scavenging ability of resveratrol. The most significant property of resveratrol is its ability to block the oxidative activity of systems with transition metal ions (Fe^{2+}/Fe^{3+}) that play an essential role in the formation of reactive oxygen species in Fenton's reactions. Resveratrol in the in vitro systems efficiently scavenges the hydroxyl radical ($OH^{\bullet}$), superoxide radical (LOO•), superoxide anion radical ($O_2^{\bullet-}$), singlet oxygen ($^1O_2$), and nitrogen oxide ($NO^{\bullet}$) **[36].** Resveratrol upregulates cellular mechanisms of oxidative resistance by inducing mitochondrial superoxide dismutase in human cells **[42].** These include mechanisms of increasing endothelial nitric oxide synthase (eNOS) expression in endothelial cells, suppression of platelet activity, activation of adenosine receptors, and general antioxidant properties. Endothelial NOS is a nitric oxide synthase that generates NO in blood vessels and is involved in regulating vascular tone by inhibiting smooth muscle contraction and platelet aggregation. Resveratrol's antioxidant activity is responsible for a whole lot of other beneficial effects to humans, including prevention of ototoxicity, diabetes and many other diseases.

ROS

Reactive oxygen species (ROS) include highly energetic, bioactive and short-lived molecules that are derived from the reduction of molecular oxygen produced in mitochondria which accumulate in the cytoplasm. Multiple endogenous enzyme systems including NAD(P)H oxidase, xanthine oxidase, myeloperoxidase, cytochrome P450 isoenzymes, lipoxygenase, cyclooxygenase, heme oxygenase, and glucose oxidase, produce variety of ROS, including superoxide, hydroxyl radical, hydrogen peroxide, peroxynitrite, hypochlorous and superoxide ($O_2^{\bullet-}$). They are responsible for chronic acid, and lipid radicals. ROS are associated with various human diseases **[43-45]** as initiators of the oxidative process **[44]** as well as in the development of certain diseases **[45]** and have varying degree ofeffect on various cardiovascular diseases. The natural antioxidant system in the human body tries to cope with ROS produced via various endogenous antioxidant enzyme systems, which include SOD, glutathione peroxidase, catalase and thioredoxin. The critical balance between ROS synthesis and the antioxidant defense system is termed as the redox system of the cell. Enhanced activity of oxidant enzymes and/or reduced activity of antioxidant enzymes lead to oxidative stress. ROS have also been shown to act as tumor promoters **[43].** SOD superoxide dismutase is the natural and the most important antioxidant defense system of combating ROS. It catalyses the dismutation of superoxide anion into oxygen and hydrogen peroxide, which are both less harmful than superoxide. Another important naturally occurring endogenous antioxidant is glutathione, which protects cells from radical damage by its radical scavenging action **[46]**. Vitamins C and E are some other exogenous antioxidants, which have been defined as "antioxidants" due to their ability to delay or inhibit oxidation.

ROS include not only the hydroxyl radical (OH^-), but also the superoxide radical ($O_2^{\bullet-}$), and hydrogen peroxide (H_2O_2). Among these, the hydroxyl radical is the most reactive chemical species. It induces some oxidative damage to almost any biomolecule it touches, such as all proteins, DNA, nucleic acids and can markedly alter protein structure **[47].** Free radicals and ROS damage these lipids by oxidation. It also encompass molecules such as fatty acids, polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA) and their derivatives (including monoglycerides, diglycerides, triglycerides and phospholipids), as well as other sterol-containing metabolites such as cholesterol **[48].** The superoxide radical anion can be dismuted by the natural antioxidant enzyme system SOD, but in vitro experiments have showed that it can combine with other ROS or RNS to form even more harmful species, the rate of reaction being faster than that with SOD **[49].** It reacts with nitric oxide to form peroxynitrite (ONOO-), which is even more harmful for biological molecules.

The H_2O_2 activity as an active oxygen species comes from its potential to produce the highly reactive hydroxyl radical through the Fenton reaction. H_2O_2 apparently does not produce free radicals on lipid peroxidation, but instead stimulates important detoxifying oxidative enzyme systems **[50].**

RNS

Reactive nitrogen species (RNS) are a family of antimicrobial molecules derived from nitric oxide (•NO)

inflammation, DNA damage, human colon carcinomas, etc. NO is formed from L-arginine by the enzyme nitric oxide synthase (NOS) which catalyses the conversion of arginine to citrulline. Nitric oxide (NO) has been implicated in a diverse collection of physiological functions including smooth muscle relaxation, inhibition of platelet activation, neurotransmission, and immune response **[50]**. It is generally produced in mitochondria in cells like ROS but macrophages and immune cells also produce large quantities of NO. Plants also produce reactive nitrogen species, either in response to stress, or as byproducts of aerobic metabolism. It serves as a signaling molecule in nervous systems in various biological pathways **[51].**

Apart from its physiological functions, NO has been shown to be involved in the pathology of many inflammatory diseases including arthritis. NO can also cause nitrosylation **[52]** and nitration of proteins **[53].**

It can also react with various heme and non-heme proteins. NO can either accelerate lipid peroxidation or terminate lipid peroxidation depending upon the concentration of ROS available **[54].** Another RNS is N_2O_3, which acts as a nitrosating agent and damages DNA by deamination **[55].** RNS act together with ROS to damage cells, causing nitrosative stress. These two species are often collectively referred to as ROS/RNS. For example, NO reacts with the superoxide radical anion in the body to form a new species peroxynitrite (PON) which is as harmful to the body as any other ROS. PON is a short lived species as compared to NO, which is relatively stable. In biological systems, it reacts with carbon dioxide to form carbonate ($CO_3^{\cdot-}$) and nitrogen dioxide ($NO_2^{\cdot}$) radicals. It oxidizes low density lipoproteins (LDL), which is the early stage of atherosclerosis. It also damages DNA strands and its reactivity is far greater than that of N_2O_3 **[56, 57].**

Oxidative & nitrosative stress

Oxidative stress occurs due to the inability of the biological system to cope with the excessive production of partially reduced oxygen species i.e. ROS. Under these conditions, biological molecules are exposed to ROS, and this leads to their oxidation, causing severe damage to these molecules or permanent cellular dysfunction. Similarly, imbalance between the production and elimination of RNS from the body causes nitrosative stress. These reactive oxygen species and reactive nitrogen species are beneficial to biological systems when available in small quantities, but prove dangerous when produced in excess, causing oxidative and nitrosative stress.

The `redox status' of a cell is an important signaling device in cellular homeostasis, and refers to the ratio of the reduced and oxidized forms of certain cellular components (e.g. NADPH/NADP, GSH/GSSH) **[36, 58]**. Oxidative stress changes the redox status of the cell and consequently alters the cellular metabolic pathways. This can cause damage to the organism, resulting in disease initiation. Oxidative damage to nuclear DNA is thought to be one cause of carcinogenesis **[59, 60, 61].**

3.2 Resveratrol as insulin mimetic

Diabetes mellitus is a modern-day epidemic, which is characterized by chronic hyperglycemia due to abnormal insulin secretion or insulin receptor or post-receptor events, affecting the overall metabolism of carbohydrates, proteins, and fats, resulting in serious complications, such as nephropathy, retinopathy, cardiovascular disease, and peripheral neuropathy. Brownlee et al. **[62]** discovered that hyperglycemia resulted in an increased production of reactive oxygen species by mitochondria via electron transport, which evokes oxidative stress that eventually results in β-cell dysfunction and finally diabetes complications.

Numerous antioxidant and anti hyperglycemic agents have been scrutinized against oxidative stress for β cell protection like N-acetylcysteine, vitamin E, metformin, troglitazone, glyclazide, etc., but prolonged administration of these drugs induces unfavorable effects, and thus a compound without any side effects, which if administered for a long period of time would be very useful in both type 1 and type 2 diabetes, is required. Resveratrol is one such naturally occurring molecule which has been found to improve insulin action in various animal models **[63].** In general, the management of diabetes involves three main aspects: reduction of blood glucose, preservation of β cells, and, in the case of type 2 diabetes, improvement in insulin action **[64].**

Palsamy et al. **[33]** and many others **[65]** assessed the antihyperglycemic and antioxidant nature of resveratrol by assessing its modulatory effects on the activities of carbohydrate metabolizing enzymes in the kidney and hepatic tissues of streptozotocin-nicotinamide-induced diabetic rats. Administration of both streptozotocin (STZ) and nicotinamide (NA) has been proposed to induce experimental diabetes in rats **[66]**. STZ is well-known to cause pancreatic β-cell damage due to the presence of 2-deoxy-D-glucose, whereas NA is administered to rats to partially protect insulin-secreting cells against STZ. The pancreatic β-cells activity is deteriorated due to its vulnerability to the free radical toxicity **[67]**. Administration of resveratrol to diabetic rats resulted in diminished levels of glycosylated hemoglobin (HbA1C). It also improved the plasma insulin level by stimulating β cells to synthesize more insulin and regulate HbA1C formation rate **[33, 34, 68].** Hence it has insulin mimetic effects. Also, oral administration of resveratrol to diabetic rats significantly

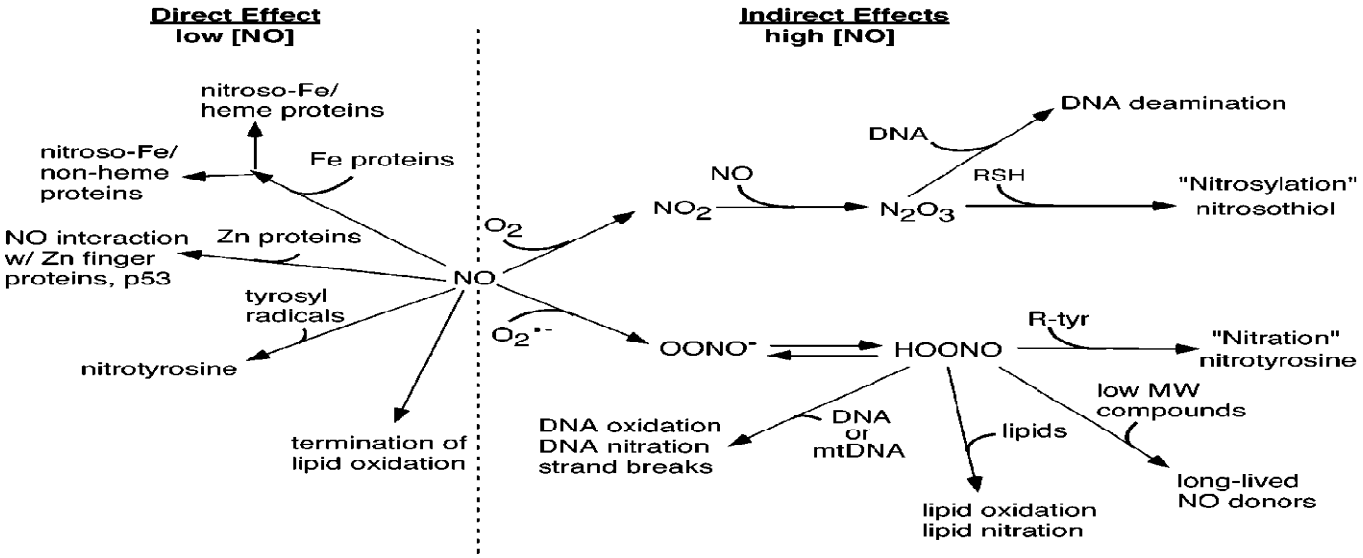

Fig.3 chemistry of NO **[50]**

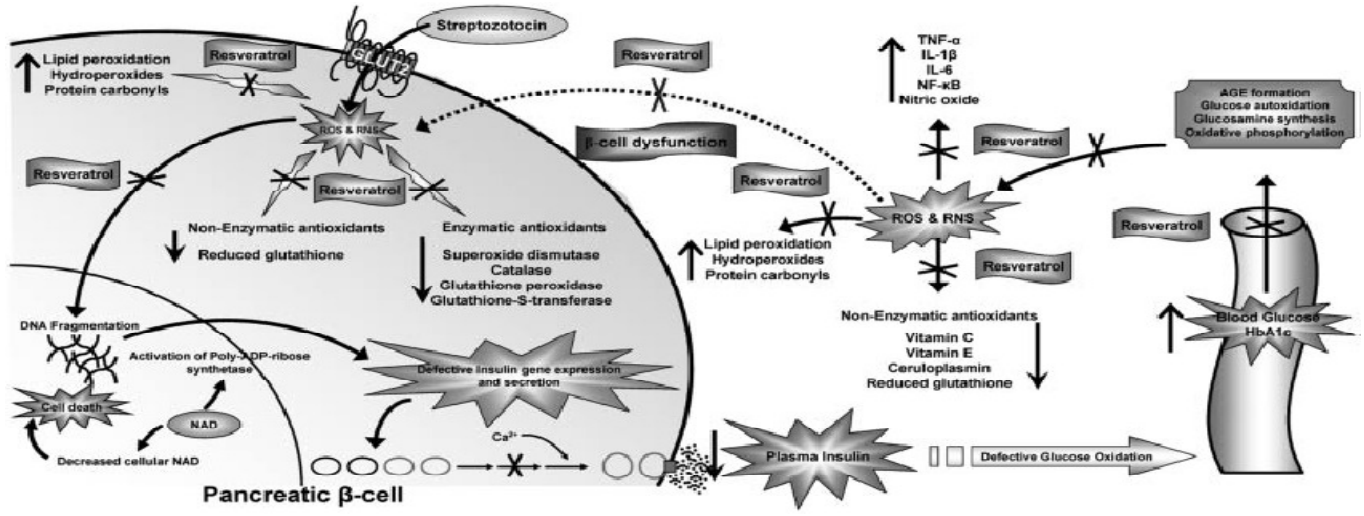

Fig. 4. Schematic representation of mechanism of streptozotocin-nicotinamide-induced experimental diabetes and the effects of resveratrol **[70]**

improved the activities of enzymatic antioxidants, which reflect their antioxidant and protective effects against oxidative stress which destroys β cells **[69,70].**

It is hypothesized from many studies that temporary resting of B cells increases their ability to secrete insulin and may delay the onset of overt diabetes. It was also found that resveratrol administration decreases insulin secretion and delays the onset of insulin resistance **[71].** It was found that in animals with hyperinsulinemia, resveratrol administration effectively reduced insulin secretion **[72-75].** Improvement of insulin action by resveratrol administration is believed to be associated with activation of the protein AMPK (activated protein kinase) and sirtuin protein. The therapeutic potential of resveratrol as an insulin mimetic is complex and involves many effects. Administration of resveratrol along with some other anti diabetic therapy can help treat diabetes.

3.3 Resveratrol as an anti cancer agent

Resveratrol holds potential as anti cancer drug. It can trigger or block cell death signaling in tumor cells depending on the dose concentration. Jang et al. **[76]** were the first to demonstrate this striking feature of resveratrol, where they showed that resveratrol possesses cancer-chemopreventive and cytostatic properties via the three major stages of carcinogenesis, i.e. initiation, promotion and progression. Resveratrol has been shown to promote apoptosis by blocking anti-apoptotic proteins expression or by inhibiting signal transduction through the PI3K (phosphoinositide 3-kinase), MAPK (mitogenactivated protein kinase) or NF-κB pathways in cancer cells **[77-79].**

The anti-carcinogenic effect of resveratrol is believed to be associated with its antioxidant activity, and it has been shown to inhibit cyclooxygenase, hydroperoxidase,

protein kinase C, Bcl-2 phosphorylation, Akt, focal adhesion kinase, NFκB, matrix metalloprotease-9, and cell cycle regulators. Many in vitro and in vivo studies provide a rationale in support of the use of resveratrol in human cancer chemoprevention in a combinatorial approach with either chemotherapeutic drugs or cytotoxic factors for the highly efficient treatment of drug refractory tumor cells **[80].** It has also been shown that resveratrol can exhibit pro-oxidant properties, leading to oxidative breakage of cellular DNA in the presence of transition metal ions such as copper. Recently, it has been proposed that such a pro-oxidant action could be a common mechanism for anticancer and chemopreventive properties of plant polyphenols.

Resveratrol against breast cancer

Estrogen has a crucial role in the development of breast cancer, and inhibition of estrogen synthesis is important for its prevention. Due to its structural similarity to the estrogen female hormone, Lu et al. **[29]** and many others demonstrated the agonist as well as antagonistic properties of resveratrol on the MCF-7 breast cancer cell line. It was found that it acts as a mixed agonist and antagonist of the estrogen receptor **[81].** It behaves as an estrogen receptor agonist in the absence of estrogen, but as an antagonist in its presence. Ruotolo et al. **[82]** in fact demonstrated the anti-estrogenic properties of its metabolite and found that no other metabolite except resveratrol-3-O-sulphate showed antiestrogenic properties. Wang & Leung **[83]** demonstrated the potent role of resveratrol as an aromatase inhibitor in estrogen synthesis. Thus resveratrol is a promising candidate for breast cancer prevention and treatment as well.

3.4 Resveratrol as an antagonist for AhR

AhRs (Aryl hydrocarbon receptors) are transcription factors that are bound to chaperones but when they bind to ligands like dioxin, they dissociate from chaperones and translocate to the nucleus, and this may change the gene transcription. Dioxins are harmful environmental pollutants, mainly emitted from industrial pollution. They have long half-life **[84]** and tend to accumulate in the body. They have many adverse health effects, including immunosuppression, carcinogenesis, cardiovascular diseases and endothelial cell damage. Casper et al. **[85]** found that resveratrol present in red wine has antagonist activity on AhR and thus it can prevent dioxin toxicity. They considered resveratrol to be a competitive antagonist against other AhR ligands like dioxin which is highly toxic and found that it has the requisite properties of potency and nontoxicity to protect against aryl hydrocarbon-induced pathology.
Cigarette smoke, which contains AhRs, is considered responsible for osteoporosis and periodontal diseases. In this regard, Singh & co-workers **[86]** investigated the direct antagonist ability of resveratrol on dioxin (TCDD) which inhibits osteogenesis. They suggested resveratrol to be a promising therapeutic agent for smoking-related bone loss. Ishida et al. **[87]** also studied the antagonistic ability of resveratrol against dioxin induced toxicity administered through different routes. They found that resveratrol injected subcutaneously has better protective action than resveratrol administered orally.

3.5 Resveratrol prevents cisplatin ototoxicity

Cisplatin is a widely used chemotherapeutic drug used in the treatment of soft tissue cancers including testis, ovary, cervix, lung, head and neck, and bladder, but it has serious adverse effects, such as nephrotoxicity, neurotoxicity, and ototoxicity. Cisplatin administration may lead to hearing problems (ototoxicity) due to functional and morphological changes in the cochlea with increasing risk of ototoxicity by high cumulative dose **[88].** Various animal and human studies of temporal bone have shown that cisplatin affects various regions of the cochlea, including the inner and outer hair cells in the basal turn, spiral ganglion cells, and stria vascularis, leading to hearing loss due to production of ROS like superoxide anion (oxidative stress), triggering cell death **[89, 90].** Ototoxicity occurs as a result of inner ear hairy cell degeneration due to oxidative processes. Several antioxidant agents have been recommended to prevent ototoxicity due to cisplatin **[91-92]**. Resveratrol has been found to have the therapeutical potential of preventing cisplatin-related ototoxicity. Erdem et al. **[93]** in their experimental rodent study investigated the potential effect of resveratrol in cisplatin related ototoxicity prevention. Seidman et al. **[94]** also demonstrated the ability of resveratrol in preventing ROS mediated noise damage to the auditory system of rats. Results have also been reported for the antioxidant efficacy of resveratrol against the toxic effects of gentamicin via protection of the organ of Corti. Thus resveratrol can prevent cisplatin induced ototoxicity.

3.6 Resveratrol as an anti inflammatory drug

COX (cyclooxygenases) are the enzymes responsible for the formation of important biological mediators called prostaglandins that cause inflammation. Presently three isoforms of this enzyme are known, namely COX-1, COX-2 and COX-3. The enzyme contains two active sites, a heme with peroxidase activity and the other is the cycloxygenase site. It catalyses the formation of prostaglandins by sequential cyclooxygenase and peroxidase reaction. Inhibition of COX can provide relief from inflammation and pain. NSAIDs (Non steroidal anti-inflammatory drugs) exert anti-inflammatory effect via inhibition of COX. Multiple

evidences are available which show that resveratrol also has cyclooxygenase (COX) inhibition property, specifically against COX-2 **[95-98].** It differentiates between two isoforms of COX. Szewczuk et al. **[99]** found that resveratrol inactivated COX was devoid of both peroxidase and cyclooxygense activity.

The feature that makes resveratrol different from other classical non-steroidal anti-inflammatory drugs (NSAID) is that it is a potent inhibitor of both the cyclooxygenase and peroxidase catalytic activity of COX-1, while NSAIDs target the cyclooxygenase reaction only **[100, 101].** The mechanism by which resveratrol selectively inhibits the cyclooxygenase and peroxidase reactions of COX-1 is still unknown.

Drakibova et al. **[102]** showed that resveratrol and related polyphenols may be suitable inhibitors of neutrophil activation responsible for acute inflammation, implying their anti-inflammatory potential. Resveratrol also inhibits the production of free radical oxygen species (ROS) via NADPH oxidase and this further correlates an anti-inflammatory mechanism **[103, 104].**

High concentrations of resveratrol have been shown to trigger apoptosis via decrease in activity and metabolite production of COX as well as affecting cell survival pathways such as p53-NFκB, MAPKs etc. and thus help in cancer prevention **[105-107].**

Szewczuk et al. **[99]** proposed that resveratrol inactivates COX-1 by a "hit-and-run" mechanism, and offers a basis for the design of future selective COX-1 inactivators that will probably act the way resveratrol does, in particular, by reacting at the peroxidase active site.

Lastra & Villegas **[5]** and many others have shown resveratrol as a beneficial agent in the control of inflammatory disorders such as arthritis and inflammatory bowel disease **[4,108].** The suggested mechanism of action include inhibition of synthesis and release of pro-inflammatory mediators, modification of eicosanoid synthesis, inhibition of activated immune cells and inflammatory enzymes **[4].**

3.7 Resveratrol in neuroprotective activity

Astrocytes are star shaped glial cells in the brain that perform many major functions such as maintaining energetic metabolism, ion homeostasis and transport of glutamate, which is the major excitatory neurotransmitter in CNS, and its excess accumulation leads to neurodegenerative disorders. Astrocytic glutamate uptake is essential for maintaining glutathione levels in the brain to combat oxidative damage caused by ROS during oxidative phosphoryation. Resveratrol is found to be effective in neuroprotective activity and this neuroprotection has been mainly attributed to its intrinsic antioxidant properties. Neuroprotective activity of resveratrol involves astrocyte activation, as indicated by the in vitro increased and decreased glutamate uptake and glutathione content in the studies conducted by de Almeida et al. **[109]**. They investigated the effect of resveratrol on primary cortical astrocytes and found that resveratrol acted in a dose dependent manner. At low concentration, it was able to increase glutamate uptake and glutathione content, while at high concentration it decreased glutamate uptake. Their findings implicated the protective role of resveratrol in brain disorders, particularly that involving glutamate toxicity. The underlying mechanisms of these changes are not clear at the moment and it is necessary to exercise caution with its administration because elevated levels of this compound could contribute to aggravate these conditions.

It was also found to be effective against ischemic brain injury and kainic acid induced seizures or neuronal cell damage in rodents **[110a, 110b].** Saravanan et al. **[111]** showed that resveratrol can delay the onset of neurodegenerative disease against β-amyloid plaque formation and oxidative stress and is ideal for treating neurodegenerative diseases. Recent evidences from in vitro and human studies suggest that oxidative stress and mitochondrial dysfunction are the main causes for the development and progression of several neurodegenerative diseases including Alzheimer's disease (AD) **[112-115].** AD is characterized by progressive loss of memory. The etiology of AD is still not completely known at present, but protein misfolding is considered to be the major reason, where some proteins (β-amyloid) abnormally fold and accumulate in the brain as plaque, which is highly neurotoxic. Oxidative stress is believed to be the reason for APP (amyloid precursor protein) alteration and hence the pathogenesis of AD **[111]**. Even the brains of AD patients are found to contain oxidative products of lipid peroxidation and DNA damage. Thus any antioxidant would help in declining plaque formation **[116-119].** Saravanan et al. **[111]** performed rodent studies of resveratrol for forty five days and found that resveratrol diminished plaque formation in brain in a region specific manner and decreased and increased levels of glutathione and cysteine, respectively. In 2005, Marambaud et al. showed that resveratrol in vitro removes amyloid deposits by increased intracellular proteosomal activity **[120].** The exact mechanism underlying reduction of plaque pathology by resveratrol in vivo is still unknown. Two probable action mechanisms have been proposed. While one mechanism advocates that the cysteine residues protect neuroblastoma cells from oxidative stress and cell toxicity and downregulates transcription of the amyloid precursor protein in human neuroblastoma cells **[121]**, another speculates that the chelating property of resveratrol as well as that of cysteine to chelate copper and zinc enriched in β-amyloids is responsible for its ability to retard plaque formation.

Owing to the rapid metabolism of resveratrol, its bioavailablity remains low despite its high oral availability. In this regard, Lu et al. **[122]** designed, synthesized and evaluated a series of resveratrol derivatives with reduced hydroxyl groups as antioxidants and inhibitors of β-amyloid aggregation, but they also found that this neurodegeneration prevention occurred without Sirt1 activation.

3.8 Resveratrol as an anticonvulsant

Status epilectus is a neurological disorder where activation of excitatory amino acid receptors triggers the formation of ROS, resulting in long lasting seizures or convulsions. Both in vivo and in vitro studies suggest that free radicals play a critical role in the enhancement of excitotoxicity **[123].** The speculated reason for the long lasting seizure is activation of the excitatory amino acid receptor that triggers the formation of reactive oxygen species (ROS), which may further release glutamate, thus forming a loop leading to neuronal death **[124-126]**. Various experimental studies demonstrate the ability of antioxidants to prevent excitotoxicity induced by agents like glutamate and domoic acid **[127-130].** Therefore, the use of antioxidants could be a potential approach in arresting or inhibiting the seizure genesis caused by excitotoxic agents like kainic acid, etc. Various experimental models of status epilectus have been developed, like lithium–pilocarpine model, kainic acid-induced model, etc. **[131-133].** Among the various models, Gupta et al. **[134]** in their rodent studies demonstrated resveratrol's ability to prevent against kainic acid induced seizures. Kainic acid is an analogue of glutamic acid which when injected systemically or intracerebrally in animals produces seizures by activation of the excitatory amino acid receptors **[131].** They found that kainic acid injection induced seizures in rats with increased levels of MDA (malondialdehyde), indicative of oxidative stress, as was expected. It was observed that a single dose of trans-resveratrol did not inhibit seizures, but increased the latency of convulsions, while when the dose was doubled, it provided significant protection against seizures. They correlated this finding with attenuation in the levels of MDA by the use of trans-resveratrol. The same group again investigated the effect of trans-resveratrol against pentylenetetrazole (PTZ) induced seizures in rats and found the same antileptic action of resveratrol **[135]**. Thus resveratrol can be concluded to have the ability to prevent seizures and act as an anticonvulsant drug.

3.9 Resveratrol as an antiviral agent

Resveratrol was found to be a potent antiviral agent against various DNA and RNA viruses **[136].** The first report of its antiviral activity came in 1999, when Docherty et al. **[137]** found that resveratrol inhibited virus replication in herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) of the Herpesviridae family of viruses in a dose-dependent manner. It was found that the resveratrol mode of action was to delay the cell cycle and, inhibit reactivation of virus from infected neurons. Apart from HSVs, other members of the Herpesviridae family have been also shown to be susceptible to resveratrol treatment. Resveratrol was also found to inhibit polyomavirus replication in the same dose dependent manner in vitro by blocking the synthesis of viral DNA **[138].** A strong antiviral activity of resveratrol has been also demonstrated against influenza virus in vitro and in vivo **[139].** Wang & co-workers **[140]** evaluated the anti HIV activity of resveratrol metabolites. The cellular pathways that lead to its protective activity are still far from being elucidated.
Besides this anti-HIV activity, resveratrol has limited toxicity, making it a strong lead compound for the development of new anti-HIV compounds that could be used alone or in combination with other drugs. Christine et al. **[141]** demonstrated the anti HIV activity of some resveratrol derivatives and their ability to enhance the antiviral activity of decitabine, a nucleoside analog that decreases viral replication by increasing the HIV-1 mutation rate. Their results indicated that the combination of resveratrol and decitabine are highly synergistic without corresponding cellular toxicity.

3.10 Resveratrol has a vasoprotective role

Endothelial NOS (eNOS), also known as nitric oxide synthase 3 (NOS3), generates NO in blood vessels and is involved with regulating vascular function. NO is an important signaling molecule. Nitric Oxide (NO) is of critical importance as a mediator of vasodilation in blood vessels. It is induced by several factors, and once synthesized by eNOS it results in the phosphorylation of several proteins that cause smooth muscle relaxation Wallerath et al. **[142]** reported that stilbene derivatives, like trans-resveratrol, stimulate acute nitric oxide (NO) release from vascular endothelial cells and induce upregulation of endothelial nitric oxide synthase (eNOS) gene expression. Thus resveratrol, by regulating NO concentration, regulates blood flow.

3.11 Resveratrol as a calorie restriction mimetic

Resveratrol gained a major popularity boost in 2003 when Sinclair and co-workers **[143, 144]** reported the ability of resveratrol to mimic calorie restriction and activate sirtuin proteins. **Dietary restriction (DR) or Caloric restriction** (CR) is a dietary regimen that is based on low calorie intake or reduction in nutrient availability without malnutrition, which has been shown to increase the life span and protect against a variety of ageing related diseases, such as Type 2 diabetes, cardiovascular diseases, cancer and neurodegeneration in

a variety of different organisms, including yeast, nematodes, fish and rodents, resulting in better health as compared to diet without calorie restriction **[144-146].** Baur et al. **[72]** in their mice studies demonstrated the beneficial effect of resveratrol as a calorie mimetic. They found that rats which were given resveratrol, along with a high fat diet, showed fewer evidence of chronic diseases as compared to rats which were given a high fat diet without resveratrol and lived the same duration as the rats which were given the control diet. If this holds true for humans, resveratrol holds the potential not only to help humans live longer, but also healthier. Thus it can be assumed that resveratrol acts as a calorie restriction mimetic. Resveratrol does not mimic all aspects of CR, such as decrease in heart rate and core body temperature **[147].** In fact, resveratrol increases the metabolic rate and fasting body temperature in mice fed a high-fat diet **[73].**

3.12 Resveratrol as an anti ageing drug

Sirtuins are class III HDACs proteins that have deacylase activity and are critical to ageing **[148,149].**They regulate important biological pathways in bacteria, archaea and eukaryotes. They have been implicated in influencing a wide range of cellular processes like aging, transcription, apoptosis, inflammation and stress resistance, as well as energy efficiency and alertness during low-calorie situations. The name Sir2 comes from the yeast gene 'silent mating-type information regulation 2', a gene responsible for cellular regulation in yeast. The well-established member of the sirtuins family, SIRT1, is the mammalian homologue of the yeast SIR2. Sirtuin activators slow down the onset of age associated diseases which reduce the rate of ageing. SIRT1 is one of the key genes upregulated during calorie restriction, which leads to a number of biological adaptations to prolong lifespan **[144].** Overexpression of sirtuin is believed to be the reason for slowing down of ageing in yeast **[150, 151].** Resveratrol has long been shown to act as an anti ageing compound due to its ability to activate the sirtuin compound **[143].** It has been reported to increase the life span of yeast, flies and several non-mammalian species, and confer protection against a variety of aging-related maladies, including neurodegenerative diseases, multiple forms of cancer and cardiovascular disease, implicating its potential as an anti-aging agent in treating age-related human diseases **[4,77,152]** Some early reports observed that overexpression or increased dosage of Sir2 increased lifespan in both Caenorhabditis elegans and Drosophila **[150,151,153,154]**. But later on it was found that increased longevity was calorie restriction mediated and increased dosage of Sir2 increased the lifespan modestly. It was observed that increased dosage of Sirt1, the mammalian ortholog closest to Sir2, does not increase the lifespan, but improves healthy aging in mice **[155].**

Sirtuin activators slow down the onset of age associated diseases which reduce the rate of ageing.
The role of resveratrol in extending lifespan is somewhat controversial, but its long term administration in mice increased their lifespan, the pattern being similar to what was observed in calorie restriction mediated longevity **[156].** AMPK maintains the energy balance of the cell by modulating ATP levels. Resveratrol activates AMPK, which in turn activates Sirtuin proteins.

3.13 Resveratrol as a signaling molecule

Some of the molecular pathways regulated by resveratrol involve stimulation of some protein complexes such as p53, NF-κB and PGC-1α. Here are some of these protein complexes which interact with resveratrol.

NF-κB

NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that controls transcription of DNA. Its incorrect regulation has been associated with cancer, inflammatory and autoimmune diseases, viral infection, and improper immune development. It is considered to be one of the key regulators of the inflammatory cellular response and it has been implicated in cellular proliferation, transformation and tumor development. NF-κB is activated by multiple stimuli, such as bacterial and viral infections. Resveratrol decreases nuclear factor kappa B (NFκB) activation **[157].** Resveratrol's blocking action of NF-κB also suppresses iNOS, COX-1 and COX-2 expression, as well as many other genes, including multiple cell adhesion molecules **[158].** Thus, resveratrol's anti-inflammatory effect is multifaceted. Cancer and other chronic diseases, such as diabetes, are associated with chronic activation of NF-κB **[159].** Therefore, its inhibition of NF-κB may reduce the effects of related chronic disease. Resveratrol's anti-inflammatory actions have been demonstrated to prevent, delay, or reduce the severity of chronic inflammatory disease in animal models.

p53

p53 is the anti-tumor protein in multicellular organisms that regulates cell cycle and prevents genome mutation and hence cancer. Thus many times it is also referred to as a guardian of genome. It is one of the main blockers of the cell cycle, leading cells to the death row. A faulty p53 is unable to suppress cell growth, which ultimately results in tumor development. Indeed, studies have shown that p53 is either defective or simply absent in most cancers **[160].** Resveratrol suppresses tumor promoter-induced cell transformation and markedly induces apoptosis, transactivation of p53 activity and

expression of p53 protein. Thus the activation of p53 can be considerd as a crucial mediator of the antiviral activity of resveratrol.

PGC-1a

By acting as a SIRT1 activator, resveratrol induces PGC-1α activity, which results in mitochondrial biogenesis in the heart, liver, brain, and skeletal muscle, although there is variation between tissues. This resveratrol mediated decrease in PGC-1a acetylation results in an increase in PGC-1a activity. PGC-1α enhances mitochondrial function and reduces oxidative stress **[161, 162].** With greater numbers of mitochondria in skeletal muscle, more oxygen can be delivered to the working muscle cells. This allows greater metabolic energy to be produced through oxidative phosphorylation and decreases oxidative stress on the muscle cells **[148].**

4.Results

This review article presents the results of recent studies investigating the pharmacokinetics, bioavailability, and toxicity of resveratrol in humans. There now exists a large body of evidence suggesting resveratrol potential to provide protection against certain human diseases, including cardiovascular disease, cancer, and degenerative neurological disorders and improve overall health. There has been sufficient evidence of beneficial physiological effect of small term dosage of resveratrol on health. But its long term administration effects still need to be elucidated on whether it will increase the lifespan in humans or not. It remains somewhat intriguing that such a structurally simple molecule as resveratrol is capable of so many health-preserving wonders. Potential side effects have been suggested if megadoses of resveratrol are used. Thus, adding red wine to the diet may be a temptation for some, while some will prefer dieting.

5.Conclusion

Resveratrol's ability to improve health and enhance life have led to huge interest of researchers and pharmaceutical companies in developing resveratrol based drugs. However, the major challenge that still prevails is that resveratrol is a multi targeting drug and the need of the hour is target specific drugs. Hence, the research still needs to focus on how to make resveratrol a target specific and fruitful drug without side effects. Various models suggest that partial inhibition of a small number of targets can be more efficient than complete inhibition of a single target. Furthermore, some studies suggest that combinatorial therapies could help design better drugs that will be directed against a particular target rather multiple targets, although there has been no report published so far regarding the toxicity of resveratrol in vivo due to its poor bioavailability. Designing a target specific drug is the challenge that still needs to be chased.

Abbreviations

TCDD-(2,3,7,8-tetrachlorodibenzo-p-dioxin), **NF-κB**-nuclear factor-kappaB, **AhR**- aryl hydrocarbon receptors, **NSAID**-non steroidal anti inflammatory drugs, **COX**- cyclooxygenases **PGC-1α** Peroxisome proliferator-activated receptor-c coactivator 1α **AMPK** AMP-activated protein kinase **ROS** reactive oxygen species **RNS** reactive nitrogen species **eNOS** endothelial nitric oxide synthase

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