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Review

Resveratrol: from enhanced biosynthesis and bioavailability to multitargeting chronic diseases

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ABSTRACT

Resveratrol, a phytoalexin with a wide range of pharmacological properties is synthesised by plants in response to stress, injury, infection or UV radiations. As it is a secondary metabolite with many health promoting properties, various methods employing microorganisms and genetic manipulation of different synthetic enzymes, have been comprehensively studied to increase its production. Its rapid metabolism and low bioavailability have been addressed by the use of bio enhancers and nano-formulations. This flavonoid is extensively researched due to its pharmacological properties such as anti-oxidative, anti-inflammatory and immuno-modulating effects. Knowledge of these properties of resveratrol has led to elaborate studies on its effect on diabetes, neurodegenerative diseases, cancer, ageing, obesity and cardiovascular diseases. At molecular level it targets sirtuin, adenosine monophosphate kinase, nuclear Factor-κB, inflammatory cytokines, anti-oxidant enzymes along with cellular processes such as angiogenesis, apoptosis, mitochondrial biogenesis, gluconeogenesis and lipid metabolism. This review discusses the properties of resveratrol and the different approaches of addressing the unfavourable synthesis and pharmacokinetics of this stilbene. Pre-clinical evaluations of resveratrol on diabetes mellitus, cardiovascular and neurological diseases are elaborately discussed and the underlying pathways involved in its therapeutic activity have been given paramount importance. Following the pre-clinical studies, clinical trials on the same reveal the efficacy of resveratrol in the effective management of these diseases. This review provides an intricate insight on resveratrol's significance from a dietary component to a therapeutic agent.

1. Introduction

Resveratrol (3,4',5 trihydoxystilbene) is a phytoalexin and a member of the stilbene family, which is commonly found in some spermatophytes. It is produced in plants in response to stress, injury, infection or UV radiations. The food sources of this flavonoid are grapes, peanuts, wine, blueberries, bilberries, dark chocolate and tea. The health benefits of resveratrol were first highlighted in the early 1990s, when it was noticed that in spite of the consumption of high fat diet the French had low incidence of coronary heart diseases. This effect was stated as the "French paradox" and the low incidence of coronary heart diseases in France was attributed to the consumption of red wine [1]. Resveratrol, a component of red wine was later credited for these beneficial effects [2].

Resveratrol exists in two isoforms, cis and trans and both these isoforms also exist as glucosides, i.e., bound to glucose. It has been observed that the trans form of resveratrol is more potent than the cis form [3]. The reason for higher biological activity of the trans form is the lower steric hindrance of substitutes in this form over the cis form. Isomerisation of trans form to cis form occurs either at a pH greater than 11 or by solar or UV radiations. Illumination of 260 nm light for 150 min leads to the conversion of 50.9% of trans-resveratrol to its cis form [4] (Fig. 1).

Resveratrol has been associated with a wide range of pharmacological properties. These pharmacological properties are attributed to the anti-oxidative, anti-inflammatory and immuno-modulating effects of this stilbene. Knowledge of these properties of the flavonoid has led to the inspection of its potential against diabetes [5–7], neurodegenerative diseases [8,9], cancer [10–12], ageing [13,14], obesity [15] and cardiovascular diseases [16,17].

2. Biosynthesis

Resveratrol is found in different food sources and is synthesised in plants by the phenylpropanoid pathway, in response to external stimuli such as UV radiations, microbial infection, fungicides, etc, and is

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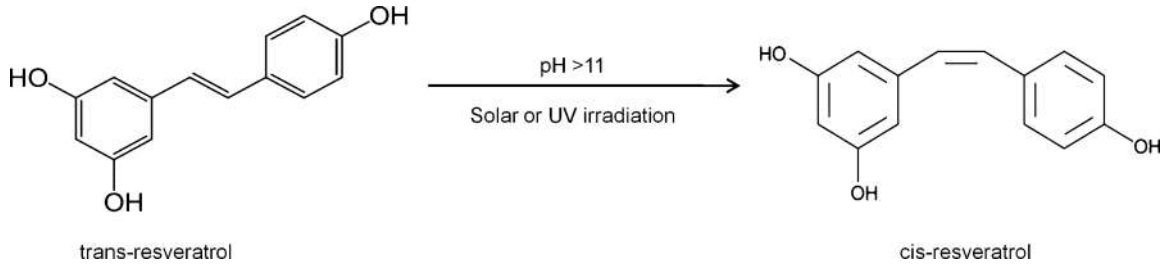

Fig. 1. pH and light induced conversion of trans to cis-resveratrol.

therefore a secondary metabolite. For the synthesis of resveratrol the phenylpropanoid pathway involves aromatic amino acids L-phenylalanine and L-tyrosine (Fig. 2) [18]. The non-oxidative deamination reaction of these amino acids by L-phenylalanine ammonia lyase and L-tyrosine ammonia lyase leads to the generation of cinnamic acid and 4-coumaric acid, respectively. Cinnamic acid is eventually converted to 4-coumaric acid by hydroxylation reaction catalysed by cinnamate-4-hydroxylase. Conversion of 4-coumaric acid to 4-coumaroyl-CoA by the enzyme 4-coumaroyl CoA ligase generates an active intermediate. This intermediate is generally used in normal growth and development of plants, but in stress conditions a portion of 4-coumaroyl-CoA is used in the production of flavonoids. Condensation of 4-coumaroyl-CoA with malonyl-CoA and its cyclisation eventually leads to the generation of the stilbene, resveratrol. This step is catalysed by the enzyme stilbene synthase.

Resveratrol is synthesised in response to stress but it is produced in very small amounts in plants as detailed in Tables 1a and 1b. Due to the health promoting properties of this secondary metabolite, various methods employing microorganisms and genetic manipulation of different synthetic enzymes, have been extensively researched to increase its production.

2.1. Resveratrol as a stress metabolite in plants

Resveratrol is generally synthesised in plants in response to some external stress and is therefore, a secondary metabolite. The different factors that contribute to its synthesis include infection, UV radiations, chemicals, salts, ozone, etc. As the plant sources of this phytoalexin are few and its production varies according to the season of cultivation, the environmental factors, etc; alterations in these stimuli can help in the enhancement of its yield.

The stress metabolite, resveratrol is produced by certain plants to prevent the growth of the invading pathogens. Grapevines such as *Vitis vinifera* and *Vitis riparia* produce the stress metabolite, resveratrol to overcome *Botrylis cinerea* (grey mould) and *Plasmopara viticola* (dowry mildew) infections, as it holds fungitoxic properties [19]. Resveratrol at a concentration of 60 mg/ml when incubated with sporangia suspensions, inhibited their germination by 75%; confirming its fungitoxic properties [20]. Apart from *Plasmopora* and *Botrylis* infection, *Rhizopus stolonifer* infection has also shown to augment synthesis of resveratrol. An exposure to the infection increases its content, which peaks after 24 h [21]. In another study to enhance the resistance of plants against fungal disease, *Vitis vinifera* was exposed to a combination of a soil bacterium B-781 (arrests fungal growth) and *Botrytis cinerea*. It was observed that resveratrol concentration reached a peak (78.3 μg/g fresh weight of leaves) after 3 days. Hence, fungal infection when occurring in combination with this anti-fungal bacteria was able to confer high level of resistance to plant species [22]. Similar protective effects have also been reported in other studies [23,24]. It has also been concluded that apart from functioning as a natural pesticide, trans-resveratrol can help in the conservation of fruits during storage. This property can be attributed to its anti-oxidative effect [23]. UV radiations, ozone and LED are some abiotic factors enhancing resveratrol synthesis in plants along with anoxia, fertilizer treatments and physical damage. Therefore apart from holding immense pharmacological properties, resveratrol also plays an important role in the management and protection of plants from external stress.

2.2. Artificial stress induced resveratrol synthesis

After the elucidation of the metabolic pathway for resveratrol synthesis other alterations for enhanced resveratrol production have also been exploited. Apart from enhancing its production in its plant sources its synthesis has also been accomplished in various micro-organisms.

Genes from phenylpropanoid pathway such as 4-coumaroyl-CoA ligase (4-CL) and stilbene synthase (STS) when assembled in *E.coli* with 4-coumaric acid in the medium has successfully been able to synthesise resveratrol (> 100 mg/L) [25]. Having an edge over the previous study, successful engineering of 4-CL and STS gene in *Saccharomyces cerevisiae* has further shown enhanced production [26–28]. This assembly was able to synthesise resveratrol with the benefit that yeast has food grade status. A number of similar studies targeting different genes and precursors have also successfully engineered plant genes in microorganisms for resveratrol synthesis (Table 2). The production was however sensitive to the origin from which the genes were isolated.

3. Bioavailability

Resveratrol has been noted for its protective role in the development of cardiovascular diseases, cancer, metabolic diseases, etc. These observations have been deduced from *in-vitro* studies primarily and *in-vivo* studies do not show similar efficacy. This observation was noted owing to the fact that resveratrol has rapid metabolism and low bioavailability. After consumption of 25 mg of resveratrol orally, < 10 ng/ml of resveratrol concentration peak was noted after 0.5 h [29].

3.1. Absorption

After resveratrol was ingested 77–80% of it was absorbed in the intestine [30]. Absorption occurs by transepithelial diffusion in a direction independent manner. Resveratrol metabolites are absorbed by active transport and in the blood stream the free form of resveratrol is bound to albumin and lipoproteins. When these complexes reach cells having albumin and lipoprotein receptors, resveratrol dissociates and is rendered free to enter cells. Hence, these complexes act as reservoirs for resveratrol and help in its distribution.

3.2. Metabolism

After consumption, the initial concentration of resveratrol was detected in the blood after 30 min and the concentration peaked after 60 min [31,32]. After ingestion resveratrol reaches the intestine and then the liver via the hepatic portal system. Metabolism of resveratrol

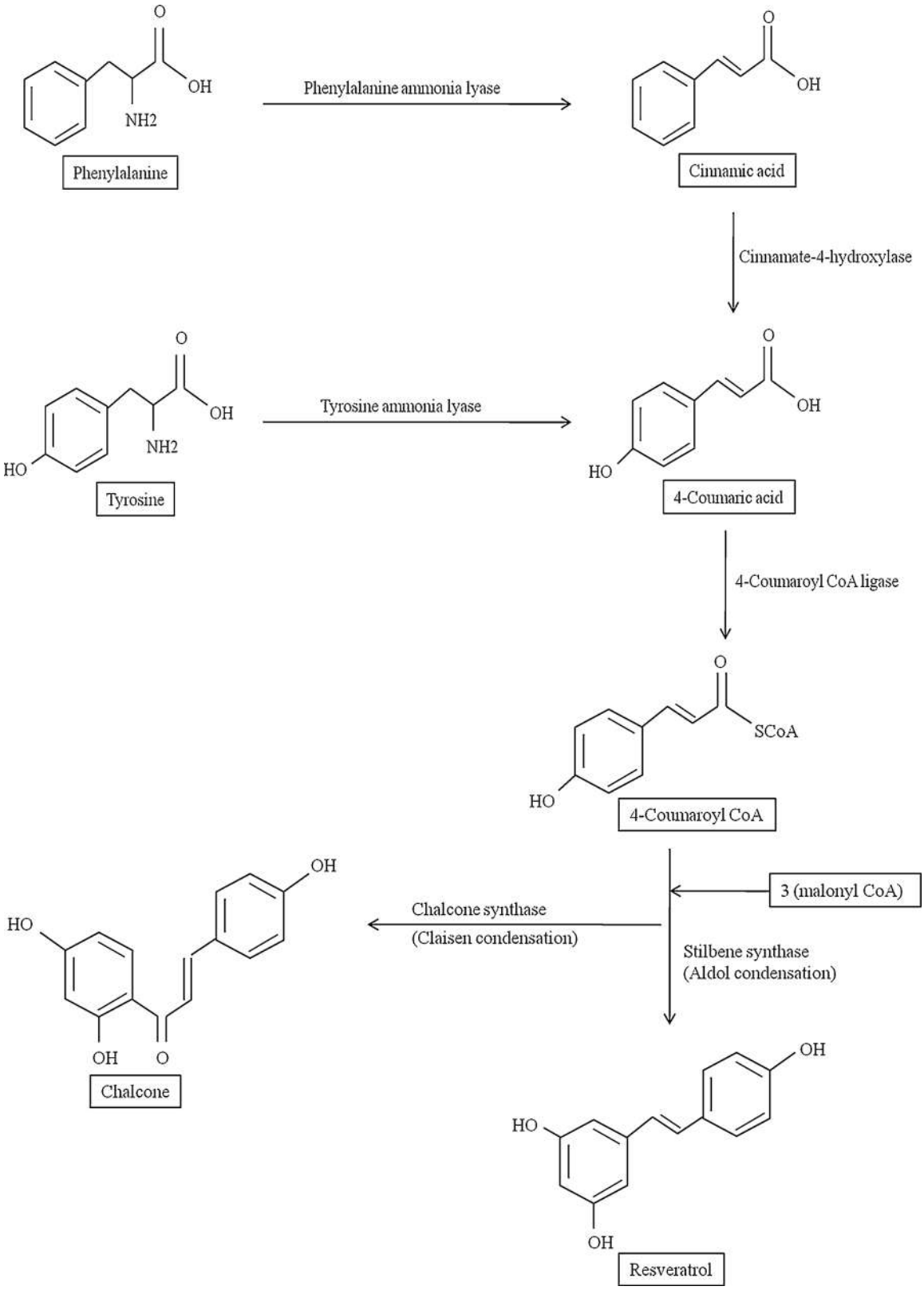

Fig. 2. Resveratrol synthesis by phenylpropanoid pathway.

occurs in the liver where phase II metabolism leads to the generation of glucouronide and sulphate forms of resveratrol employing enzymes UDP-glucuronosyltransferases and sulfotransferases, respectively [33]. Later another metabolite of resveratrol, dihydro-resveratrol was also detected in the rat urine and plasma [34].

3.3. Excretion

Along with rapid metabolism resveratrol also undergoes rapid excretion. 77–80% of the resveratrol consumed is absorbed in the intestine and 49–60% of this is excreted in the urine. Hence 75% of the total

Table 1a
Amount of trans-resveratrol in common food sources [172].

	Food source	Amount (μg/g fresh weight)
1.	Black grapes	0.5 ± 0.0
2.	Itadori root	523 ± 1
3.	Peanuts (boiled)	5.1 ± 2.8
4.	Peanut butter	0.3 ± 0.1

Values are expressed as weight ± SEM.

Table 1b
Amount of trans-resveratrol in selected beverages [172].

			Amount (μg/100 ml)
1.	Red wine	Pinot Noir, 1994 (California)	1057 ± 60
		Cabernet Sauvignon, 1996 (Bulgaria)	672 ± 10
		Merlot, 1994 (Chile)	48 ± 1
		Cabernet Sauvignon, 1995 (California)	53 ± 1
2.	Itadori tea		68 ± 1

Values are expressed as μg/100 ml ± SEM.

resveratrol consumed is excreted [30]. The remaining amount of resveratrol is metabolised and the highest concentration of free resveratrol that has been noted is 1.7–1.9% [35].

As stated earlier a peak in the resveratrol concentration was obtained 60 min after consumption. In another finding it was noted another surge in resveratrol concentration was noted after 6 h. This surge was attributed to the enteric recirculation of the metabolites formed earlier. These metabolites are reabsorbed after they undergo hydrolysis to the free form in the intestine [35]. Studying the metabolism of resveratrol it can be stated that it undergoes rapid absorption after consumption. In spite of the rapid absorption of resveratrol its levels have very low range owing to its rapid metabolism.

4. Bioenhancers

Oral administration of resveratrol encounters high metabolism leading to low levels of free resveratrol in the serum. It has been reported that a combination of polyphenols (as reported in wine) enhance its bioavailability. Some studies have determined the effect of fed or fasted conditions and the effect of different food consumed along with resveratrol supplementation but no substantial result could be interpreted [36,37].

Addressing the first barrier encountered by resveratrol in an *in-vivo* model, to attain the results achieved in *in-vitro* studies, two different experiments were conducted. The low solubility associated with resveratrol is due to its non-polar nature. Attempts have been made to increase its solubility and hence improve its absorption. Hydroxypropyl-β-cyclodextrin was used and combining resveratrol to the hydrophobic center cyclodextrin improved the solubility of resveratrol by 60,000 fold and increased its absorption as well. Though an increase in the minimal plasma concentration was obtained but no influence on its bioavailability was noted [38]. Another attempt to increase the solubility of resveratrol was the patented formulation of resveratrol SRT501. SRT501 contains resveratrol micronized to a particle size $< 5\,\mu m$. This formulation increased the surface area for absorption owing to which the peak plasma levels increased from 538 ng/ml to 1942 ng/ml. Increasing the solubility of resveratrol in the two studies produced different effects on the plasma concentration. These finding point to the fact that there may be an optimal solubility required for gastrointestinal absorption.

Resveratrol consumption is followed by its entry into the hepatic portal system leading to its metabolism and escaping the entry to this system may increase free resveratrol levels. Intravenous administration [39] and oral transmucosal delivery [40,41] have shown an increase in free resveratrol levels but these methods have also been associated with rapid clearance due to its distribution into tissues and phase II metabolism to its sulphate conjugates [33,42].

Avoiding the portal system did not show much promise in maintaining high resveratrol levels. Another issue that could be addressed was preventing resveratrol from metabolism by inhibiting glucouronidation and sulphation. Resveratrol when consumed with piperine showed a 1000% increase in peak plasma levels [43]. This increase was observed due to the decrease in the glucouronide metabolite formation, by inhibiting the enzyme uridine 5'-diphospho (UDP) glucouronyltransferase. Another phenolic compound quercetin, which inhibits sulfotransferase 1A1 (SULT1A1) enzyme activity and is therefore, known to decrease the sulphate conjugate of resveratrol. But the inhibition of this metabolite formation did not show improvement in resveratrol bioavailability [44].

An approach to prevent resveratrol metabolism by masking the prime targets of metabolism i.e. the hydrophilic hydroxyl group of resveratrol has also shown promise. Masking these hydroxyl groups with acetyl group and formation of 3,5,4'-tri-O-acetylresveratrol (taRES) led to an increase in area under the curve (AUC), thereby decreasing elimination [45].

Another aspect to address the rapid metabolism of resveratrol is increasing the stability and bioavailability by nanoformulations. These nanoformulations increase resveratrol's solubility and increase tissue absorption [46]. Lipid core nanocapsules have shown better tolerance and increased concentration in different organs like brain, liver and kidney [47]. Resveratrol-bovine serum albumin nanoparticles when injected intraperitoneally in ovarian cancer model have also shown higher concentration of resveratrol in blood and an increased distribution in liver, heart, kidney and ovaries [48].

Different methods including enhancement in solubility, altering the mode of administration, preventing metabolism and preparation of nanoformulations for increasing resveratrol levels have been attempted. All these methods have been tested on animal models but their effect have not extensively been studied in humans. Hence elaborate work still needs to be done on these enhancement protocols to attain those pharmacological effects of resveratrol that have been observed in *in-vitro* analysis.

5. Resveratrol as a therapeutic agent

Resveratrol has gained significant attraction and is a drug of interest due to its multi-target approach. As a multi-target drug it helps in regulating various alterations associated with a disease, unlike specific target drugs. Moreover, the multi-target approach helps to overcome the drawback of resistance that is associated with specific target drugs [49]. A multi-target drug interacts with several targets hence; this

Table 2
Resveratrol synthesis in various organisms by genetic manipulation.

S. No.	Organism	Genes altered/inserted	Precursor	Amount produced	Reference
1	*Saccharomyces cerevisiae*	TAL, 4-CL, RS, AR04, ARO7, ACC1	glucose or ethanol	415.65 and 531.41 mg L^{-1}, respectively	[173]
2	*Saccharomyces cerevisiae* (SC FY23)	4CL216 and vst1	4-coumaric acid	0.61 to 1.38 μg l^{-1}	[26]
3	*Escherichia coli*	4CL1 and STS	4-coumaric acid	> 100 mg/L	[25]
4	*Saccharomyces cerevisiae*	4CL1 and STS	4-coumaric acid	6 mg/L	[28]
5	*Escherichia coli*	4CL1 and STS	carboxylic acids	171 mg/L	[174]

interaction has low affinity unlike single target drugs. Owing to the low affinity, these drugs have lower range of side effects [50].

Resveratrol is a drug known for various pharmacological properties such as anti-inflammatory, anti-oxidative, anti-ageing, anti-diabetic, neuroprotective, etc. The efficacy of this phytoalexin involves various mechanisms such as the activation of sirtuin 1 (SIRT1), antioxidant enzymes, activation of nuclear factor erythroid 2–related factor 2 (Nrf-2)- KEAP1 - kelch-like ECH-associated protein 1(Keap1) mechanism, modulating nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB), inducible nitric oxide synthase (iNOS), cycloxygenase (COX), etc. The activation of sirtuins is associated with deacetylating activity thereby leading to the alteration in expression of various downstream regulators [51].

Metabolic syndrome accounts for various conditions such as hypertension, hyperglycemia, obesity, hyperlipidemia, etc which increase the susceptibility of an individual to the development of cardiovascular diseases, diabetes and stroke. A significant number of pre-clinical and clinical studies have proved the potential of resveratrol in the management of metabolic syndrome. The properties of resveratrol such as mimicking calorie restriction, enhancing energy expenditure by mitochondrial biogenesis, decreasing fat accumulation in liver and activating SIRT1 are associated with the above stated properties [52]. A further elaborate evaluation of the different metabolic targets of resveratrol and its protective role in diabetes, cardiovascular diseases and neurological diseases has been proved [53] and is discussed underneath.

5.1. Diabetes

Diabetes mellitus is characterised by the presence of a number of metabolic diseases which leads to an increase in blood sugar. Different studies have been carried out to determine the promising effect of resveratrol on diabetes and on the different organs involved in the disease [54].

Pancreatic beta cell destruction by the immune system is the prime manifestation of type 1 diabetes mellitus. Therapeutic agents reducing their apoptosis and improving the cell survival hold immense potential in the management of diabetes. Resveratrol aids in preventing cell death and increasing cell survival by different mechanisms. It has been documented that resveratrol combats oxidative stress, thereby inhibits oxidative stress induced beta cell damage [55–57]. Another mechanism of reduction in beta cell death by resveratrol has been proven by its ability to inhibit caspases and poly ADP ribose polymerase (PARP) cleavage [58]. Inhibition of PARP prevents the cells from undergoing ATP and NAD^+ depletion and eventually protecting cells from necrosis. Apart from preventing cell death in pancreas resveratrol also ensures cell survival by decreasing the levels of glucose hence, eliminating the various diabetic complications arising from hyperglycemia [59]. Inhibition of chemokine receptor 6 (CCR-6) expression, which leads to the prevention of inflammatory cell migration was another manifestation of resveratrol administration, which increases beta cell number [60].

The term ‘diabesity’ has been coined considering the strong association of obesity with type-2 diabetes [61]. It is the excessive accumulation of adipose tissue in obesity which leads to the release of fatty acids, contributing to inflammation and insulin resistance [62,63]. Adipose tissue also executes an endocrine role releasing adipokines which further contribute to inflammation and insulin resistance [64]. Resveratrol decreases proinflammatory cytokines [65] and macrophage infiltration [66], challenging the first contributor to the association. It has also proven to have inhibiting effect on adipokines thereby, further leading to the reduction in inflammation and insulin resistance [65]. Not only does resveratrol inhibit the diabetes inducing effects of obesity but it also increases adipose tissue metabolism by increasing the activity of lipogenic enzymes [66], affects gut microbiota and satiety [67]. The improvement in tissue metabolism contributes to energy metabolism by increasing mitochondrial biogenesis. In addition to these factors, resveratrol also improves insulin sensitivity via upregulation of SIRT1 and adenosine monophosphate-activated protein kinase-α (AMPK-α) phosphorylation activity [68,69].

Skeletal muscles and liver are primary store house of glucose and muscles alone can store 3–4 g glucose per 100 g of wet muscle [70]. Insulin assisted translocation of glucose by glucose transporter type 4 (GLUT4) leads to the storage of glucose in muscles. An alteration in the transporter has been documented in type-2 diabetes which leads to an increase in glucose level in blood and eventually causing hyperglycaemic manifestations. [71]. Resveratrol has shown to increase the expression and the translocation of the transporter GLUT4 thereby increasing the transport of glucose in the muscles [72]. Apart from GLUT4, estrogen receptors are a key regulator in mediating insulin dependent and independent glucose uptake and resveratrol supplementation also modulates their expression [73]. Resveratrol regulates energy metabolism in muscles by increasing mitochondrial biogenesis and improves mitochondrial β-oxidation [74]. Improvement in mitochondrial β-oxidation lowers the lipid content which itself helps in overcoming insulin resistance [75].

SIRT1 a prime target of resveratrol in different tissues is also activated by its treatment in muscles. Its activation affects different targets such as peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) (regulates cellular energy metabolism) [14], inflammation and oxidative stress [76]. Inflammation's contribution to insulin resistance and to chronic diseases in humans has been well documented. [77]. Resveratrol has a significant effect in combating inflammation by inhibiting COX-1 and regulating prostaglandian synthesis [78]. It is also a potent inhibitor of NF-κB and inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [79]. Deletion of insulin receptor substrate-2 (IRS-2) causes hyperglycaemia and resveratrol treatment also shows promise by increasing their levels [80].

Hyperglycemia leads to compensatory hyperinsulinaemia which eventually causes insulin resistance, oxidative stress and inflammation which leads to tissue damage and in this scenario; liver is one of the most susceptible organs. Diabetes is associated with non alcoholic fatty liver disease [81]. Resveratrol addresses different malfunctions that the liver undergoes during diabetes by decreasing blood glucose level by down regulating GLUT2 expression on liver [82]. Oxidative stress is regulated by increasing the levels of anti-oxidant enzymes [83], while inflammation is reduced by decreasing levels of proinflammatory cytokines [84]. It holds potential in managing non alcoholic fatty liver disease by activation of 5' AMPK-SIRT1 [85] which regulates fatty acid metabolism thereby normalizing the levels of lipids in the liver [86,87]. Resveratrol also helps in energy metabolism by regulating mitochondrial biogenesis [14]. Different proteins involved in downstream processing of insulin pathway such as insulin receptor substrate-1 (IRS-1), Akt, phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) are also positively affected [88] (Fig. 3).

The prime manifestation of diabetes is hyperglycemia, which leads to glycation i.e. the non-enzymatic formation of adduct between glucose and plasma proteins. These proteins tend to lose their prime functions due to alterations in their naive conformation [89]. The advanced glycation end products (AGEs) are responsible for different manifestations associated with diabetes, such as retinopathy, neuropathy, nephropathy, cardiomyopathy, etc [90]. Resveratrol treatment has been linked with the reduction in AGEs related complications of diabetic nephropathy. A 45 day treatment of 5 mg/kg body weight of resveratrol in Wistar rats decreased the associated structural alterations and renal hypertrophy. It also reduced oxidative stress and apoptosis in these animals [91]. Along with kidney, resveratrol is also proven to benefit the liver by decreasing the expression of receptor for advanced glycation end products (RAGE) and improving the antioxidant profile [92]. In another study, resveratrol use has shown to inhibit the formation of bovine serum albumin (BSA) protein associated AGEs [93]. Hence, it can be concluded that resveratrol holds immense potential in mitigating the manifestations associated with AGEs formation in diabetes.

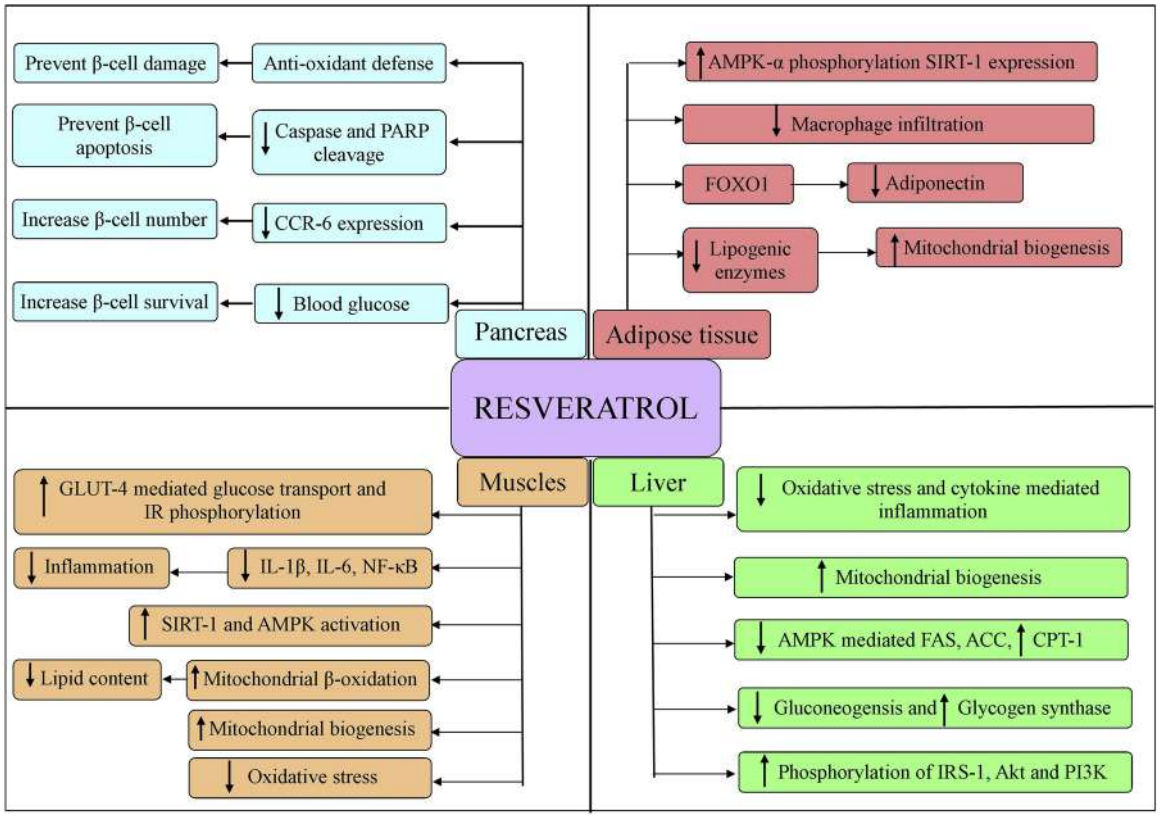

Fig. 3. Resveratrol mediated regulation of diabetes in pancreas, adipose tissue, muscles and liver.

Table 3
Summary of the clinical trials of resveratrol on diabetic patients.

Dose	Subjects	Clinical Outcome	Reference
3 x 500 mg/day	24	Decrease weight, BMI, fat mass, waist circumference, insulinogenic index	[94]
500 mg/day	194	Increases pentraxin 3 and total antioxidant status	[95]
2 x 480 mg/day	43	Improves periodontal status	[96]
75 mg/day	36	Improves neurovascular coupling and cognitive performance	[97]
2 x 5 mg/day	19	Decreases oxidative stress and improves insulin sensitivity via Akt pathway	[98]
250 mg/day	62	Improves glycemic control	[175]
2 x 500 mg/day	14	No effect on glucagon like peptide-1	[101]
3 gm/day	10	Increase SIRT-1 and AMPK expression	[99]

After support from preclinical studies the effects of resveratrol have been extended to diabetic patients. In a randomised clinical trial [94] treatment of diabetic patients with 500 mg resveratrol, thrice daily for 90 days, showed decrease in weight, BMI, fat mass, waist circumference and insulinogenic index. Resveratrol has also shown to regulate diabetes by increasing pentraxin 3 and by improving the total antioxidant status in patients [95]. Apart from these resveratrol treatment in diabetic subjects had positive consequences in periodontal status [96], neurovascular coupling and cognitive performance [97]. Resveratrol has shown optimistic effects in regulating diabetes by improving insulin sensitivity. This improvement has been accounted to the modulation in cellular pathways such as Akt [98] and increasing SIRT-1 and AMPK expression [99,100]. Unlike the positive effects that resveratrol treatment has shown, a study stated that when 14 patients with type-2 diabetes were treated with 500 mg resveratrol, twice daily, they showed no improvement on glucagon like peptide-1 secretion [101]. Hence, no effect on gastric emptying and insulin secretion were observed. This study stated that resveratrol treatment showed no improvement in diabetic subjects (Table 3).

Considering the amount of supporting data obtained from preclinical studies, the potential of resveratrol has not been extensively evaluated in clinical studies. Hence, resveratrol might have far-reaching effects in managing diabetes if further clinical evaluations are carried out. Moreover considering the bioavailability of the polyphenol, obtaining and optimising the desired results might be another challenge.

5.2. Cardiovascular diseases

According to WHO estimates, cardiovascular diseases are the leading cause of death worldwide, claiming 15 million lives in 2015. It contributes significantly to the socio-economic burden borne by different countries [102,103]. Lifestyle and dietary modifications are a prime focus in regulating this ever increasing contributor to the mortality rate every year. A diet rich in plant based foods containing dietary fibres, polyphenols, antioxidants, etc has been documented to significantly reduce the risk to cardiovascular diseases [104,105]. The role of resveratrol, a phytoalexin found in common food sources, has long been reported in the French paradox. Wine consumption decreases the rate of mortality due to cardiovascular diseases by 24–31% [106], owing to the fact that wines are rich in flavonols such as resveratrol. These positive effects of resveratrol are accounted not only because of its ability to reduce atherosclerosis but because it also decreases platelet

aggregation [1,107]. The other pharmacological properties that are associated with resveratrol are attributed to its ability to regulate oxidative stress, inflammation, vasodilation, apoptosis, platelet aggregation, etc.

Oxidative stress holds a significant role in the implications of cardiovascular diseases hence, a potent anti-oxidant holds potential in its management [108]. Compilation of several studies has demonstrated that resveratrol has multiple targets to combat an increase in oxidative stress during cardiovascular diseases. It is known to scavenge free radicals by inhibiting peroxiredoxin-2 or by undergoing its own oxidation [109,110]. Resveratrol combats oxidative stress by the stimulation of the anti-oxidant enzyme manganese-superoxide dismutase (Mn-SOD) via SIRT1 activation, hence suppresses oxidative stress induced cell death of cardiomyocytes [111]. In another study resveratrol increases the levels of the anti-oxidant reduced glutathione via AMPK and Akt pathways which eventually decreases cardiac myocyte hypertrophy [112]. Both these pathways also regulate transcription factors such as Nrf-2, the major regulator of cytoprotective responses to oxidative stress [113], ultimately reducing the amount of lipids peroxidised. Apart from regulating oxidative stress both these pathways also decrease ATP consumption and regulate hypertension via inhibition of angiotensin II mediated mechanisms [114].

Prolonged stress leads to abnormal cell death, which causes various manifestations linked to cardiovascular diseases [115]. Studies on resveratrol have shown that it is associated with the management of stress induced cell death. Regulation of cAMP/AMPK/SIRT1 and activation of Akt and B-cell lymphoma 2 (BCl-2) [116] are prime modes by which resveratrol regulates autophagy. A high fat diet induced autophagy can also be partially reversed by resveratrol supplementation [117] hence, regulating high fat induced cardiovascular manifestations. Apart from managing cell death resveratrol regulates angiogenesis via enhanced expression of vascular endothelial growth factor (VEGF) and fetal liver kinase 1 (Flk-1) to maintain sufficient blood flow to prevent myocardial damage [118].

Another aspect that a fine remedial agent for management of cardiovascular diseases should possess is anti-inflammatory properties which could prevent inflammation associated damage of myocardiocytes. Resveratrol has been associated with this property due to its ability to regulate inflammatory cytokines and inhibiting nucleotide-binding domain and leucine-rich repeat containing (NLR) proteins 3 (NALP 3) inflammasome formation [119]. An association between lipids and heart diseases has been certain for more than half a century and therapeutics having lipid lowering effects, hold promise for treating such ailments. Resveratrol has long been known for decreasing the levels of low density lipoproteins (LDL) and increasing high density lipoproteins (HDL) [120,121]. It has also been known to decrease the formation of foam cells [122] (Fig. 4).

After asserting the cardioprotective role of resveratrol on preclinical studies, a number of clinical trials have been carried out.

5.2.1. Coronory artery disease

In a study on 75 coronary artery patients resveratrol treatment was given in the form of grape extract along with 8 mg resveratrol. This treatment led to an increase in anti-inflammatory adiponectin and altered transcription factors and genes which affect inflammation. It hence, modulated the key player of cardiovascular diseases i.e inflammation. It also benefited by preventing thrombogenic plasminogenic activator type-1 and inhibiting atherothrombotic signals in peripheral blood mononuclear cells (PBMCs) [123].

5.2.2. Angina pectoris

In another randomised clinical trial, angina pectoris patients were given resveratrol in combination with calcium fructoborate. Treatment decreased the inflammatory biomarker C-reactive protein (CRP) and also the N-terminal prohormone of brain natriuretic peptide (BNP). It therefore, has beneficial effects for patients with angina pectoris [124].

5.2.3. Post infraction

Apart from coronary artery disease and angina pectoris resveratrol has also proved to be beneficial for post infraction patients. In a study on post infraction patients resveratrol treatment improved left ventricular diastolic function, endothelial function, decreased LDL and prevented unfavourable hemorheological changes [125].

5.2.4. Hypertension

Along with the posing health benefits for patients with cardiovascular diseases resveratrol has also proved beneficial for individuals having risk factors for cardiovascular diseases. In a double blinded, placebo controlled, cross trial of 18 hypertensive subjects, 60 mg resveratrol was given in combination of extracts (grape seed and skin, green tea, quercetin, ginkgo biloba and bilberry) for 28 days. Subjects after treatment showed decrease in diastolic pressure by enhancing endothelial nitric oxide synthase and nitric oxide production. No change in systolic pressure and serum-angiotensin converting enzyme activity was observed [126].

A study conducted on 59 subjects with hypertension and dyslipidemia showed that resveratrol treatment aids in vasorelaxation and decreases endothelial dysfunction by increasing NO synthesis and combating Nrf-2 mediated oxidative stress. Resveratrol treatment did not show any promise in regulating acetylcholine vasorelaxation in individuals undergoing thyroid surgery [127].

In another study the effect of the intake of 8 mg/day of resveratrol containing grape extract for 1 year was determined on the PBMCs of 35 hypertensive males with type-2 diabetes mellitus. This treatment regulated inflammation in the subjects by decreasing pro-inflammatory cytokines and altering microRNA involved in inflammation. This treatment also showed immunomodulating effects in the patients [128].

5.2.5. High risk subjects

Individuals with hypertension, hypercholesterolemia, diabetes, obesity, smoking and high age group individuals are at a higher risk of developing cardiovascular diseases. Resveratrol treatment has also shown prospects in these individuals who are at high risk for developing cardiovascular diseases. In a study, 75 patients undergoing primary prevention of cardiovascular diseases were enrolled for a triple blind randomised trial and were treated with grape supplement with 8 mg resveratrol for 6 months, followed by double dose of resveratrol for the next 6 months. Treatment decreased inflammatory markers in consideration i.e. IL-6, TNF-α, CRP and increased anti-inflammatory marker, IL-10. The treatment also increased adeponectin levels and decreased the level of soluble intercellular adhesion molecule-1. Resveratrol also demonstrated its ability to increase fibrinolysis by decreasing plasminogen activator inhibitor type-1. Hence, the anti-inflammatory and fibrinolysing tendency of resveratrol prove the therapeutic potential of resveratrol for individuals at high risk of cardiovascular diseases [129].

Apart from resveratrol supplementation the role of resveratrol in diet has also been elucidated. In a study on 783 men and women of $\geq$65 years in the Chianti area of Italy it was noted that resveratrol consumption in standard western diet was not associated with alteration in inflammation, cardiovascular diseases, cancer and mortality [130]. Contrary to the above finding a study with 1000 participants from Spain who were at high risk of cardiovascular diseases and consumed Mediterranean diet showed that the concentration of total urinary metabolites of resveratrol is directly associated with improvement in HDL, plasma triglycerides, heart rate and fasting blood glucose. Hence, the inclusion of resveratrol in diet helps to decrease the risk of cardiovascular diseases [131].

5.2.6. Atherosclerosis

In another study where 75 statin treated patients for primary cardiovascular disease prevention were treated with a capsule containing 350 mg/day of resveratrol enriched grape extract for 6 months. The

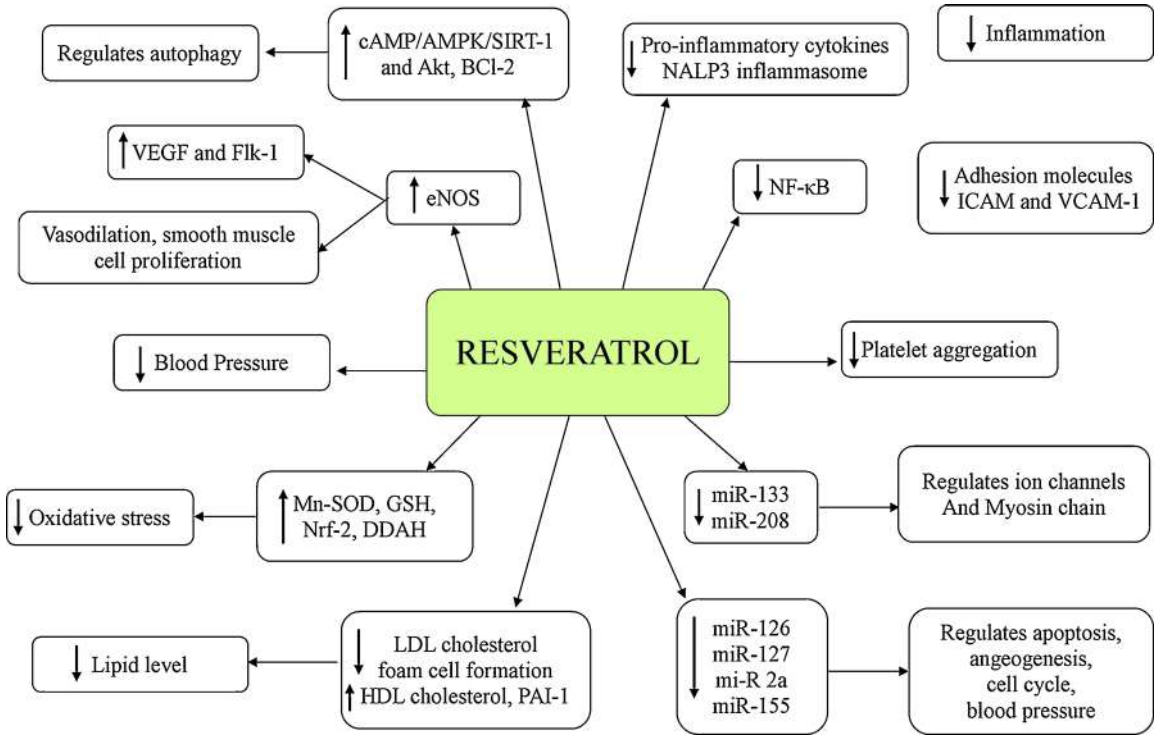

Fig. 4. Therapeutic targets of resveratrol to prevent cardiovascular diseases.

decrease in atherogenic markers (LDL, cholesterol, apolipoprotein B, oxidized lipoprotein) proved the cardioprotective role of resveratrol in primary cardiovascular disease prevention [132].

In two separate studies the effect of resveratrol in relaxing endothelial cells has been observed. Endothelial cells when cultured with plasma from resveratrol fed individuals showed decrease in adhesion molecules, IL-8 and interferon-γ (IFN-γ), proving its atherosclerosis protecting role [133]. Vascular rings obtained from 38 male patients who had undergone coronary artery bypass operation exhibited nitric oxide mediated vasodilation after resveratrol treatment. This ability of resveratrol to relax endothelial cells shows its potential in preventing atherosclerosis [134].

5.2.7. Low risk subjects

31 patients who had at least one risk factor for cardiovascular disease consumed bilberry juice for 4 weeks. They encountered decrease in CRP, IL-6, IL-15, monokine induced by IFN-γ (MIG) and an increase in TNF-α. All these are NF-κB transcription factor target genes. Hence, resveratrol also revealed its property to decrease NF-κB related inflammatory markers in subjects who were at high risk of cardiovascular diseases [135].

5.2.8. Obese and ageing subjects

Resveratrol treatment has not been efficacious in obesity and ageing population. In a randomised, placebo-controlled crossover study of 45 overweight and slightly obese men and women with mean age of 61 ± 7 years, 150 mg/day of resveratrol treatment did not alter metabolic risk markers such as apoA-1, apoB-1, cholesterol, LDL cholesterol, triacylglycerol, glucose, insulin, inflammation and endothelial function. Hence, resveratrol did not prove beneficial in individuals at risk of developing cardiovascular diseases due to obesity and age [136]. (Table 4).

Summarising the findings acquired from preclinical studies it is affirmed that resveratrol targets platelet aggregation, inflammation, oxidative stress, lipid levels, angiogenesis, autophagy, blood pressure and energy metabolism. It is hence a potent therapeutic agent in treatment of cardiovascular diseases. Compiling the clinical trial data of patients with cardiovascular diseases and healthy individuals, resveratrol has shown to reduce inflammation; blood pressure, fibrinolysis, atherosclerotic signals, lipids and it cause immunomodulation. Though resveratrol has shown promising effects on patients and healthy individuals, no effect of resveratrol were observed on different cardiovascular diseases risk markers in ageing and obese individuals. Extensive study hence needs to be done to further evaluate the effects of resveratrol and to determine its non-responsiveness on the ageing population.

5.3. Neurological disorders

Neurological disorders are a significant contributor to the burden of diseases that the developing countries bare, with the treatment cost for these diseases and disorders being $1.5 trillion in US alone. Different neurological disorders such as stroke, epilepsy, dementia, alzheimer disease, etc are one of the highest causes of death and disability in adults and are a significant contributor to constrain and dependency for working age individuals. Phytochemicals are promising therapeutic agents to tackle these diseases and the effect of resveratrol has been studied on different neurological disorders such as alzheimer's disease, parkinson's disease, etc. To study the prime targets of resveratrol, its effect on two diseases has been illustrated in this review.

5.3.1. Parkinson's disease

Parkinson's disease is a movement disorder affecting 1% of the population above the age of 60 years and it has three cardinal signs: tremor, rigidity and bradykinesia. The main hallmarks of the disease include loss of dopaminergic neurons in the substantia nigra [137] and owing to the cytoprotective properties of resveratrol it holds potential against this main hallmark. Resveratrol is an AMPK and SIRT1 activator, which in turn induces apoptosis for efficient clearance of misfolded proteins or injured mitochondria [138]. AMPK and SIRT1 are also activators of PGC-1α which enables mitochondrial biogenesis and regulates oxidative stress [139]. Resveratrol also regulates cell death by modulating apoptotic proteins Bax and Bcl-2 [140] and causes the release of astroglia-derived neurotrophic factors, brain-derived

Table 4
Summary of the clinical trials of resveratrol on cardiovascular disease patients, high risk individuals and healthy subjects.

Manifestation	Dose	Subjects	Clinical Outcome	Reference
Coronary artery disease	Grape extract + 8 mg/day resveratrol	75	Decreases inflammation and inhibits atherothrombotic signals in PBMCs	[123]
Angina pectoris	20 mg/day resveratrol + calcium fructoborate	87	Decreased inflammatory biomarkers and N-terminal prohormone of BNP	[124]
Post infarction patients	10 mg/day	40	Improved left ventricular diastolic function, endothelial function, decreased LDL and prevented unfavourable hemorheological changes.	[125]
Hypertension	60 mg resveratrol in combination with different extracts	18	Decrease in diastolic pressure, enhancement in endothelial nitric oxide synthase and nitric oxide production	[126]
Hypertension with type-2 diabetes mellitus	8 mg/day	35 males	Decreased inflammation and immunomodulatory effects.	[128]
Undergoing primary prevention of cardiovascular diseases	8 mg/day for 6 months, 16 mg/day for next 6 months	75	Anti-inflammatory and fibrinolysis	[129]
statin treated patients of primary cardiovascular diseases prevention	350 mg/day of resveratrol enriched grape extract	75	Decrease in atherogenic markers	[132]
At least one risk factor for cardiovascular diseases	Bilberry juice	31	Decrease NF-κB related inflammatory markers	[135]
Ageing and obese individuals	150 mg/day	45	No alteration in lipids, inflammation, glucose and endothelial function	[136]
Ageing individuals	Western diet	783	No association with inflammation, cardiovascular diseases, cancer and mortality	[130]
High risk of cardiovascular diseases	Mediterranean diet	1000	Improvement in HDL, plasma triglycerides, heart rate and fasting blood glucose	[131]
Healthy subjects	400 mg trans-resveratrol, 400 mg grapeskin extract, and 100 mg quercetin	44	Decrease in adhesion molecules, IL-8 and IFN-γ	[133]
Coronary artery bypass	70 μM	38 male	nitric oxide mediated vasodilation	[134]

neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) on dopamine neurons thereby, promoting the survival of neurons and oligodendrocytes [141]. Apart from promoting cell survival directly resveratrol treatment also regulates secondary factors such as oxidative stress and inflammation which are contributors to the disease pathogenesis. Oxidative stress is regulated by decreasing the levels of reactive oxygen species (ROS) and promoting anti-oxidant enzymes hence, decreasing lipid and protein oxidized products [142]. Inflammation is regulated by decreasing the levels of inflammatory cytokines and levels of COX-2 [143,144] (Fig. 5a).

5.3.2. Alzheimer's disease

Alzheimer's disease is one of the most common neurodegenerative diseases in the elderly. The disease progression is associated by the accumulation of amyloid-β (Aβ) peptides [145] and other misfolded proteins such as tau protein (microtubule-associated protein). The accumulation of these peptides eventually leads to cell death and its associated manifestations such as dementia and behavioural changes [146]. These manifestations are brought about due to the triggering of oxidative stress and inflammation [147–150]. Resveratrol addresses the different aspects that lead to the manifestations in this disease. It reduces oxidative stress by inhibiting the level of ROS, increasing glutathione peroxidase, superoxide dismutase [151] and reduced glutathione levels. A decrease in amount of lipids peroxidised also confirms decrease in oxidative stress [152]. Decrease in inflammation was noted due to decrease in inflammatory cytokines such as TNF-α, IL-6 [153] and IL-1β. Transcription factors and enzymes such as NF-κB [153] and COX-2 are also targeted to combat inflammation by resveratrol. Apart from preventing cell death by regulating inflammation and oxidative stress, this polyphenol also inhibits caspase-3 [154] and increases Bax/Bcl-2 [155]. Resveratrol is known to inhibit β-amyloid aggregation, deposition and causes their degradation and scavenging [156]. β-amyloid-induced cell apoptosis is also inhibited [157] hence, eliminating the root cause of the disease. Its treatment also modulates tau protein acetylation and phosphorylation [158], preventing the misfolding of the protein. It therefore holds immense potential in the management of alzheimer's disease pathology (Fig. 5b)

Resveratrol is known for its anti-ageing properties due to calorie restriction like effects. It activates SIRT1, prevents oxidative damage and decreases senescence and apoptosis [159]. Resveratrol's take on other neurological disorders is due to its anti-oxidative, anti-apoptotic, anti-inflammatory and cognitive and motor enhancement properties [160].

Supporting evidence from pre-clinical studies different clinical trials have also been undertaken.

5.3.2.1. Alzheimer's disease. A randomised, placebo controlled, double blind phase 2 trial on 119 patients with mild to moderate alzheimer's disease was conducted. The patients were started with 500 mg resveratrol or placebo orally per day for 52 weeks. The dose was increased by 500 mg every 13 weeks. Treatment led to an increase in ventricular volume and decrease in brain volume in comparison to placebo. Cerebrospinal fluid (CSF) Aβ40 and plasma Aβ40 levels declined in the treated group while, there was no effect on CSF Aβ42 and plasma Aβ42. This phase 2 trial concluded that resveratrol crossed the blood brain barrier and affected the central nervous system and was safe and well tolerated by alzheimer's patients [161].

5.3.2.2. Schizophrenia. Patients with schizophrenia being overweight or obese are highly susceptible to cardiovascular diseases, hence, have high mortality rate. As resveratrol has shown to reduce obesity, a study was conducted to determine the effect of the same on serum glucose and cardiovascular diseases in schizophrenia [162]. 19 men aged 18–65 years were treated with 200 mg/day of resveratrol or placebo. This treatment did not alter body weight, waist circumference, glucose and total cholesterol but it was successfully able to prevent lipid profile

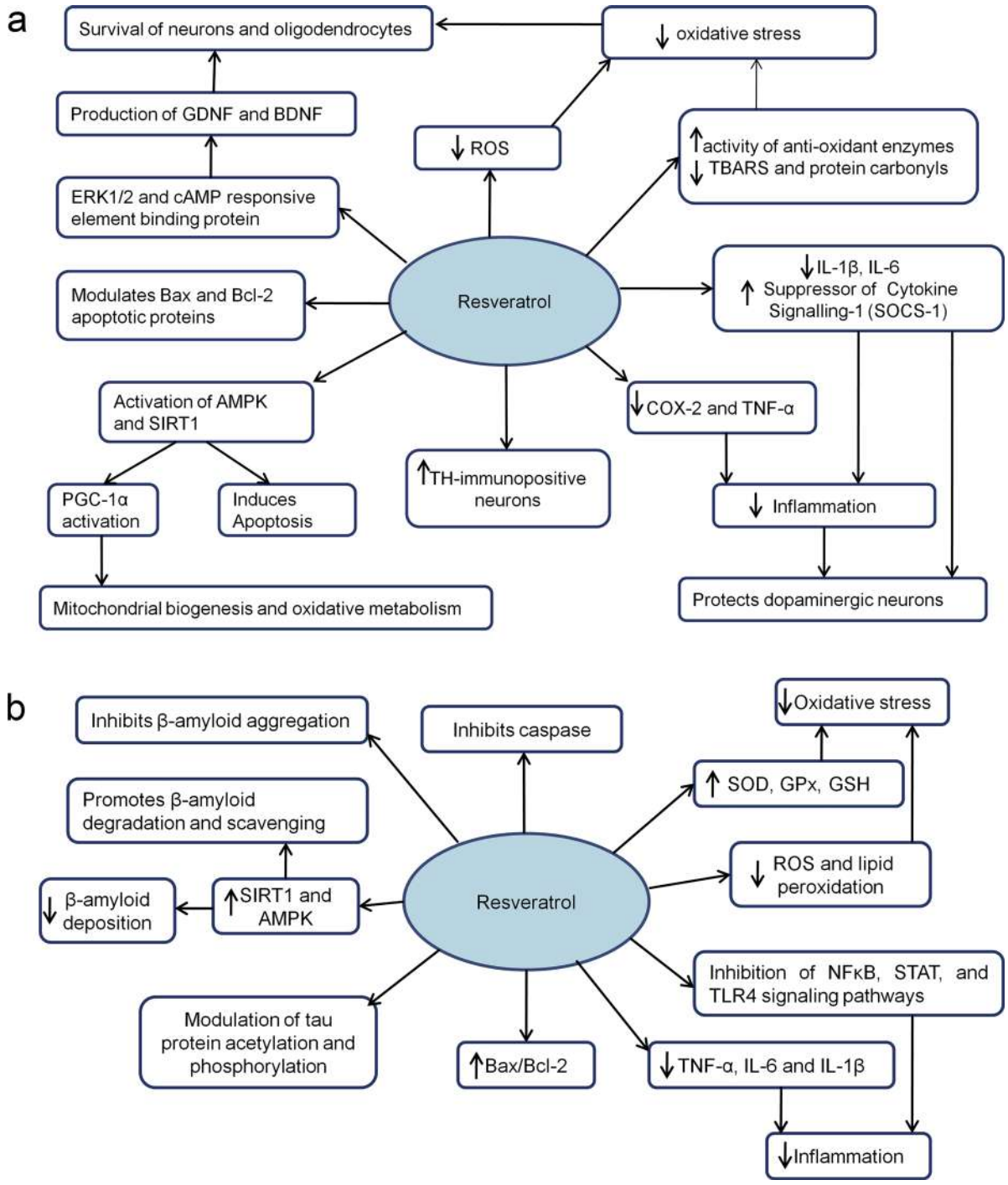

Fig. 5. (a) Protective effect of resveratrol on parkinson's disease. (b) Protective effect of resveratrol on alzheimer's disease.

damage and affected lipoprotein metabolism. Hence, resveratrol proved beneficial in mitigating cardiovascular diseases in schizophrenic patients.

5.3.2.3. Amyotrophic lateral sclerosis (ALS). Neurotoxic property of CSF from ALS patients has been reported in a number of studies and this neurotoxicity has been attributed to the high glutamate concentration in ALS/CSF. [163] Culturing the cortical motor neurons with ALS/CSF decreased that viability by 82%, proposing that this neurotoxicity was independent of glutamate. CSF from these patients also augmented the basal Ca^{2+} concentration and increased Ca^{2+} levels have been associated with apoptotic neuronal death. Culturing cortical motorneurons with CSF from ALS patients and 0.3 μM of Resveratrol alone and in combination with riluzole showed that resveratrol alone prevented the augmentation of Ca^{2+} and caused notable protection against ALS/CSF neurotoxicity. Resveratrol hence shows potential in therapeutics in ALS.

5.3.2.4. Stroke. Strokes are the third most frequent cause of death in death in US, killing a person every 6 s. Recombinant tissue plasminogen activator (r-tPA) is at present the most effective treatment for brain ischemic stroke but this treatment has a setback that it has a 3 h therapeutic time frame, restricting its clinical efficacy. In rat model of ischemia delay in treatment causes hyperperfusion leading to

extracellular matrix degradation by matrix metalloproteinases (MMPs) and ultimately causing disruption of blood brain barrier. Decreasing MMPs can help to improve therapeutic outcome. Co-administration of resveratrol with r-tPA to patients who receive late treatment significantly decreased MMPs (MMP-2 and MMP-9) hence, showed improvement in NIH stroke scale assessment [164]. Resveratrol hence increases the clinical therapeutic window of r-tPA and shows prospects in treating stroke patients receiving late treatment.

5.3.2.5. Postmenopausal women. As estrogen plays an important role in cerebrovasculature its decline after menopause increases the risk of cognitive decline and dementia in women. 47% of the women develop dementia by the age of 85 years. Hence, an early intervention to prevent dementia is necessary to enable postmenopausal women to live an independent life. In a randomised, double blind, placebo controlled trial on 80 healthy postmenopausal women, proved that dietary intake of resveratrol (75 mg twice daily) affected brain function. After 14 weeks of supplementation, enhancement in mood and cognition was reported due to enhancement in cerebrovascular perfusion. It helped to ameliorate the risk of developing dementia in women at high risk i.e. post menopausal women [165].

In another trial supplementation of equol and resveratrol to healthy menopausal women experiencing hot flashes, anxiety and depression symptoms were studied. 60 menopausal women aged 50–55 years were given 200 mg of fermented soy (10 mg equol and 25 mg resveratrol) for 12 weeks. Apart from improvement in vaginal dryness, heart discomfort and sexual problems, this treatment also significantly improved work and activities. Women also showed significant improvement in sleep domain hence, this treatment led to a significant improvement in the life quality of menopausal women [166]

5.3.2.6. Ageing. As ageing progresses hippocampus shrinks and leads to memory impairment and diet alteration has show to have beneficial effects on brain ageing. A trial determined the effect of resveratrol on memory performance in ageing subjects [167]. 23 healthy overweight and ageing (50–75 years) individuals were treated with 200 mg/day of resveratrol for 26 weeks. This treatment led to significant improvement in functional connectivity of the hippocampus (prime region associated with memory function). Apart from this, the treatment also decreased glycated haemoglobin (HbA1c), body fat and increased leptin; thereby, improving glucose metabolism. This study stated that resveratrol treatment played an important role in maintaining a healthy brain during ageing (Table 5).

5.3.2.7. Healthy individuals. A number of studies have been conducted to determine the effect of resveratrol on cerebral blood flow and cognition in healthy individuals. It has been determined that resveratrol treatment did not affect cognition [168,169] and blood pressure [169,170] in healthy individuals. Its treatment led to an increase in cerebral blood flow [169–171] and enhanced oxygen extraction [168].

Summarising the findings from a number clinical trials it can be stated that resveratrol holds great potential in the management of a number of neurological diseases. It beholds similar effects during clinical trials on human subjects and also shows prospects in managing manifestations associated with menopause and ageing. Hence, resveratrol is an appropriate therapeutic agent to cope with the different neurological diseases and disorders and its properties should to be further explored.

6. Discussion

Studies dating from early 1900s recognised the potential of resveratrol as a therapeutic agent. Ever since its discovery, there have been an expanding amount of preclinical studies suggesting that resveratrol has a wide range of pharmacological properties. Translating the promising results from basic science to clinical studies is a challenge, owing to resveratrol's pharmacokinetics i.e., its rapid metabolism and poor bioavailability. There are different solutions to enhance the bioavailability of resveratrol, such as nano-formulations, bioenhancers and phytochemical combinations. These solutions still need immense exploration as very little work has been investigated on humans. Approaches to tackle the low synthesis of this secondary metabolite have also been explored, by using microorganisms and genetic manipulation of its synthetic enzymes. Determining its effect on multi-targeting chronic diseases, clinical trials conducted on diabetes, cardiovascular diseases and neurological diseases were elaborated in this review. Clinical trials on diabetic subjects showed immense potential, by improving insulinogenic index, BMI, peridontal status, antioxidant levels and neurovascular coupling. Studies on obese and overweight individuals did not produce similar effect as 4 trials observed no effect of resveratrol on insulin sensitivity. Treatment of patients with cardiovascular diseases (coronary artery disease, angina pectoris, post infarction patients and hypertensive subjects), high risk and healthy individuals showed successful management of diastolic function, inflammation, endothelial function, lipoprotein levels, hemorheological changes, nitric oxide production and fibrinolysis. Resveratrol hence, served as a potent cardioprotective agent in all the trials but two separate trials conducted on ageing and obese individuals provided conflicting results, as no positive effects could be associated with the treatment. Determining its effect on neurological manifestations, resveratrol's treatment for alzheimer's disease, schizophrenia, amyotrophic lateral sclerosis and stroke proved beneficial. Postmenopausal women and ageing subjects supported the previous results as both these trials proved effective. Compiling the effects of the studies on all three chronic diseases suggests that considering the vast amount of preclinical data supporting resveratrol's benefits, clinical trials are very few and they still need elaborate exploration to determine the trend of resveratrol's effects. Considering the trials conducted on diabetic and cardiovascular disease subjects, studies on ageing and obese population did not produce similar results. This aspect alone needs intricate inspection to understand resveratrol's therapeutic potential. As

Table 5
Summary of the clinical trials of resveratrol on neurological manifestations.

Disease	Dose	Subjects	Clinical Outcome	Reference
Alzheimer disease	500 mg/day to 1000 mg twice daily	119	Safe and well tolerated. Crossed the blood brain barrier to affect CNS	[161]
Schizophrenia	200 mg/day	19 men	Prevented lipid profile damage and affected lipoprotein metabolism aiding cardiovascular disease prevention	[162]
Amyotrophic lateral sclerosis	0.3μM	29	Augments Ca^{2+} concentration and provides protection against ALS/CSF neurotoxicity	[163]
Stroke	Adjuvant with r-tPA	–	Increases clinical therapeutic window of r-tPA and manages stroke	[164]
Postmenopausal women	75 mg twice daily	80	Enhanced mood and cognition. Decreased risk of developing dementia	[165]
Postmenopausal women	200 mg fermented soy (25 mg resveratrol + 10 mg equol)	60	Improved dryness of vagina, heart discomfort, sexual problems, sleep domain, work and activities	[166]
Ageing	200 mg/day	23	improved functional connectivity of hippocampus and glucose metabolism	[167]

preclinical studies prove the synergistic effect of resveratrol with other phytochemicals, clinical data still need validation is this regard on human trials. Hence, pharmaceutical efforts to validate resveratrol's potential needs to be elaborately determined to reap the range to health promoting benefits that resveratrol has to offer to healthy as well as health compromised individuals.

Conflict of interest

The authors declare that they have no conflict of interest.

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