

**Recent Advances of Resveratrol as Add on Therapy: Review article****Mona Adly<sup>a\*</sup>, Reham A.M. Ellisy<sup>a</sup>, Ahmed Nouredin Hassan<sup>b</sup>**<sup>a</sup>Medical Pharmacology Department, Faculty of Medicine, South Valley University, Qena, Egypt.<sup>b</sup>Clinical Pharmacology Department, Faculty of Medicine, Galala University, Suez, Egypt.**Abstract**

**Background:** Resveratrol (RV) is a widely-known polyphenolic chemical found in many plants, including berry, peanut and grape fruits. It is well known for its association with numerous health benefits, including glucose metabolism optimization, anti-obesity, cardio protective, neuroprotective, anti-cancer activities, antiaging and neurodegeneration prevention. These promising therapeutic effects are controlled by a number of interconnected mechanisms that regulate oxidative damage, cell death and inflammation. As a result, it is possible that RV might be regarded as a great nutraceutical and pharmacological therapeutic supplementary medication.

**Objectives:** This review would broaden understanding of RV and motivate researchers everywhere to take RV into consideration as a pharmaceutical treatment to treat and protect against numerous diseases in the future. Our review article will cover the potential of this unique natural chemical to become an important nutraceutical and therapeutic add on medication. Also, the toxicity, side effects and drug interactions of RE is gathered and analyzed in this article.

**Conclusion:** This research implies that there is still more to learn about RV.

**Keywords:** Resveratrol; Add on therapy; Nutraceutical; Anti-inflammatory; Antioxidant.

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## 1. Introduction

Resveratrol is a phytoalexin, which is present in many plants, including peanuts, berries and grapes, and was originally discovered in 1940 from *Veratrumgandiflorum*, or white hellebore plant (Aggarwal et al.,2004). Large amounts of RV were found in diseased, damaged, and ultraviolet-treated leaves (Nawaz et al., 2017).RV is a nutraceutical that researches has been focused upon because of its multiple bioactivities and powerful pharmacological aspects, including anti-oxidative (Meng et al., 2018), anti-

inflammatory (Nuneset al., 2018), cardiovascular protective (Duthie et al., 2000) and anti-aging properties (De La Lastra and Villegas, 2005).

## 2. Chemistry

Resveratrol is a stilbenoid polyphenol, which is made up of two phenolic rings that are joined by a double styrene bond to produce the compound 3, 4', 5 trihydroxystilbene, it has a molecular weight of 228.25 g/mol. As shown in (Fig. 1) , it has two isomers cis- (Z) and trans- (E) due to the double bond. The trans isomer when exposed to UV radiation undergoes isomerization to cis isomer (Malviyaet al., 2022).

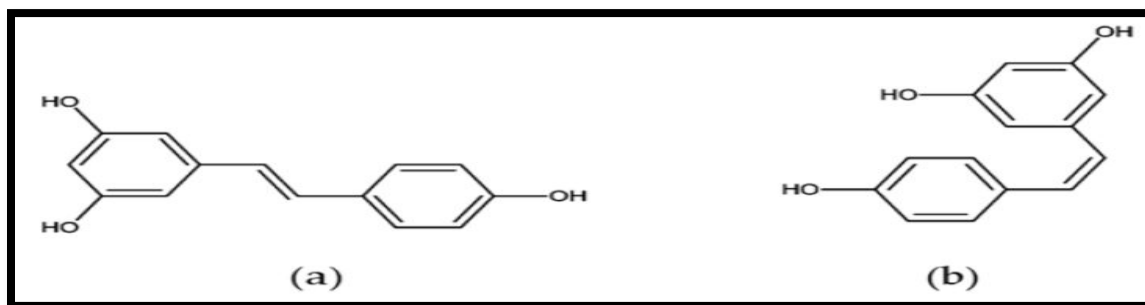


Fig.1. Structure of trans-resveratrol (E) a and cis resveratrol (Z) b (Meng et al., 2021).

## 3. Mechanism of action

There are various suggested means forestations. Genetic RNA is necessary for bioactivity as these molecules bind the amino acids and transport them to the protein-synthesis site where they can be integrated into the newly formed protein. TyRS, a definite tRNA that carries tyrosine to the site of protein synthesis, is impacted by RV. RV binds to TyRS rather than tyrosine when it is synthesized in greater quantities, as in the case of stressful conditions. The RV-TyRS complex goes to the nucleus activating the poly (ADP-ribose) polymerase-1 (PARP-1) protein there. This protein is widely recognized to be essential for stress response and DNA repair. When

activated, PARP-1 turns on a network of genes that shields the cell from harm brought on by stress. The genes contain the p53 tumor suppressor gene, which blocks the release of inflammatory substances like interleukin-6, and the longevity genes Forkhead box class O 3a (FOXO3A) and Sirtuin 6 (SIRT6) (Bele and Khale, 2013).

Resveratrol also activates the sirtuin enzymes, most predominantly the SIRT1 enzyme activated by resveratrol and other sirtuin activating compounds (Malviyaet al.,2022).This enzyme's activation results in an increase in mitochondrial activity, an increase in aerobic capacity and a promotion of oxidative de-phosphorylation. The genes

act as a crucial to generating homeostasis and regulating energy as a result of the SIRT1 impact (Stivala et al., 2001).

#### 4. Resveratrol pharmacokinetics and bioavailability

As regards to RV absorption, the enterocyte apical membrane allows for passive diffusion or carrier-mediated transport, which is subsequently rapidly and extensively converted to resveratrol glucuronides or sulphates (Lancon et al., 2004). The colon receives around 90% of the supplied RV in its intact form, where it undergoes gut fermentation. After being

absorbed by the portal vein, the produced polyphenolic metabolites are further methylated, glucuronidated, or sulfated in the liver. When the metabolites enter the systemic circulation, target tissues and cells, their physiological importance can be seen (Meng et al., 2021). In the liver, RV is hydroxylated to piceatannol as shown in (Fig.2), which can be released into the blood stream and then conjugated to produce piceatannol sulfates or piceatannol glucuronides, that come back to the gut (Pasciu et al., 2010).

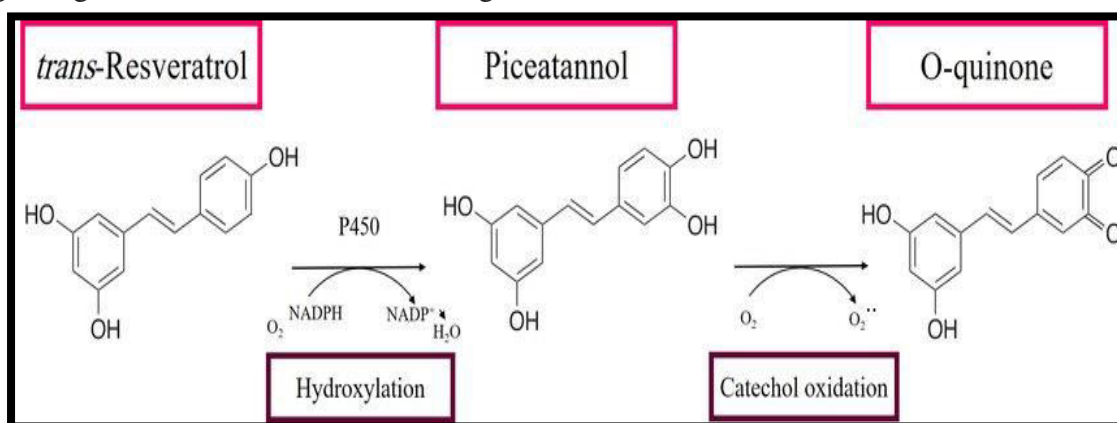


Fig.2. Metabolism of resveratrol in the liver (Pasciu et al., 2010).

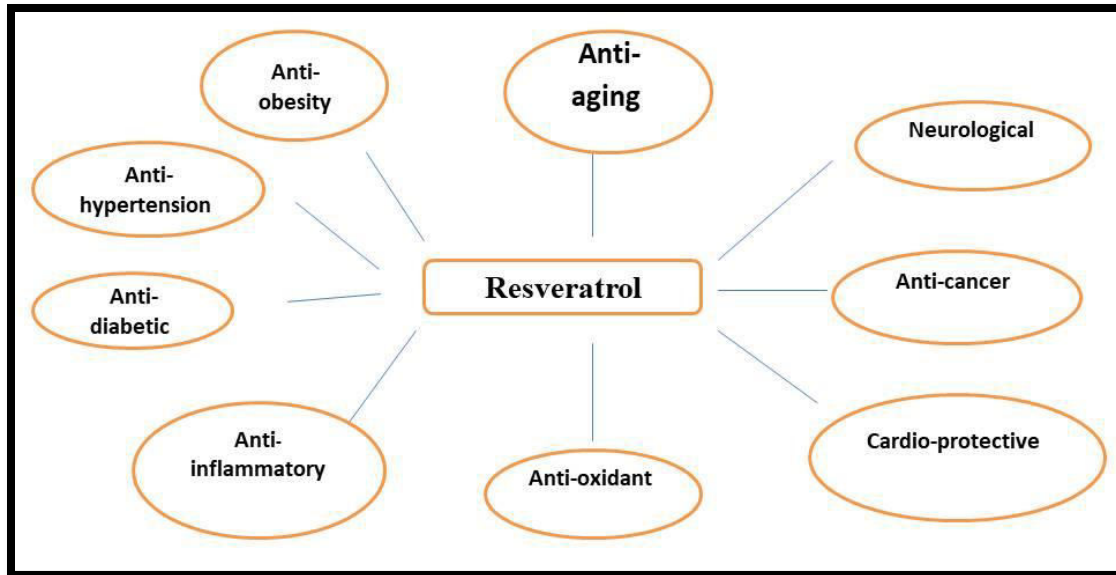
Resveratrol and unneeded metabolites can be eliminated by urine or recycled back to the small intestine through the bile (Gowd et al., 2019).

Using RV *in vivo* has significant disadvantages, including rapid absorption, poor bioavailability, and limited water solubility (Ferraz da Costa et al., 2020). As a result, many methodological techniques have been employed to enhance the poor

aqueous solubility and the limited bioavailability of RV, including the use of solid lipid nanoparticles and nanostructured lipid carriers (Chimento et al., 2019).

#### 5. Biological activities of resveratrol

As shown in (Fig.3 and Table 1) RV has many biological activities.



**Fig.3.Resveratrol biological effects.**

### 5.1. Anti-diabetic roles

Diabetes mellitus (DM) is one of the most prevalent metabolic disorders which is associated with alterations in carbohydrate, protein and fat metabolism (Dilworth et al., 2021).

Diabetes mellitus incidence has been continued to rise globally due to the high prevalence of people's lifestyle changes and obesity(Grill ,2020). Diabetes is characterized by elevated blood glucose levels and various complications, including cardiomyopathy, atherosclerosis, nephropathy, erectile dysfunction, endothelial dysfunction, neuropathy and retinopathy (Zharkikh et al.,2020).RV has been suggested as a dietary supplement for delaying the development of DM pathogenesis since it significantly lowers DM risk and its related complications(Spínola et al.,2019). RV improves glycemic control and reduce glycated hemoglobin (HbA1c) levels when used daily for 3 months. Additionally, RV

lowers total cholesterol, total protein and systolic blood pressure. This demonstrates that RV may be used as an adjuvant medication for the treatment of DM. (Berman et al.,2017).

### 5.2. Anti-Inflammatory role

Inflammation is an adaptive reaction, which can be triggered by a number of risk factors: including microbial invasion or tissue damage (Medzhitov, 2008).Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns(DAMPs), respectively, are names for the exogenous and endogenous signaling molecules (Iwasaki and Medzhitov, 2015).

Different pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), are capable of identifying both PAMPs and DAMPs (Fitzgerald and Kagan, 2020). Intracellular signaling cascades, including those involving kinases and transcription factors, are brought about by PRR activation. For the development of

inflammation, the signaling pathways previously stated can promote the production of a range of inflammatory mediators (such as cytokines)(Singh et al.,2020).

Resveratrol inhibits a number of signaling pathways, such as the nuclear factor kappa B (NF- $\kappa$ b) (Adhami et al., 2003), arachidonic acid (AA) pathway (Li et al., 2018), activator protein-1(AP-1) (Manna et al., 2000) and mitogen-activated protein kinase (MAPK)to exert its anti-inflammatory effects(Pirola et al., 2008).

### 5.2.1. Arachidonic Acid Pathway

Phospholipase A2 cleaves membrane phospholipids to liberate AA, which is then metabolized by cyclooxygenase enzyme (COX) to produce PGs (such as PGD<sub>2</sub>, PGE<sub>2</sub>, and PGI<sub>2</sub>) and thromboxane (TX) A<sub>2</sub> (Chandrasekharan et al., 2002).

Resveratrol produce an anti-inflammatory response through inhibition of the functions of COX. Resveratrol has an ability to distinguish between two COX isoforms has also been demonstrated, indicating that it is a weak suppressor of COX-2 peroxidase activity, the isoform that non-steroidal anti-inflammatory drugs target, but is a strong suppressor of COX-1 catalytic activity (Kundu et al.,2006).

### 5.2.2.Nuclear factor kappa B Pathway

Numerous pro-inflammatory mediators, including tumor necrosis factor-alpha (TNF- $\alpha$ ) and interleukin 1 beta (IL-1 $\beta$ ), can be stimulated byNF- $\kappa$ b(Su et al.,2022).

Resveratrol has an anti-inflammatory properties because it can decrease the

activation of NF- $\kappa$ B-induced inflammatory factors (Zheng et al.,2013).

In the endothelial cells, RV has been shown to increase the expression of Kruppel like factor 2 (one of the transcription factor subclasses belonging to the zinc-finger family that is involved in the control of cellular differentiation and growth)and reduce the synthesis of inflammatory chemicals such TNF- $\alpha$ ,IL-1 $\beta$ , vascular cell adhesion molecule 1, and intercellular adhesion molecule 1 (Chu et al.,2018).

Resveratrol acts as an immune modulator and has an anti-inflammatory properties via activating Sirt-1 (Saiko et al.,2008). As a deacetylase, Sirt-1 is essential for immunological tolerance (Gao et al.,2012), because it blocks the TLR-4/NF- $\kappa$ B/STAT pathway, which results in a reduction in the generation of inflammatory factors (Wiciński et al.,2018).

### 5.2.3. Mitogen-activated protein kinase

Translocation of MAPK to the nucleus leads to phosphorylation of a number of target transcription factors, such as NF- $\kappa$ b, AP-1 and nuclear factor E2-related factor 2 (Nrf2)(Meng et al.,2021).MAPK signal transduction pathways are essential for a variety of biological activities as: differentiation, proliferation, inflammation, apoptosis and responses to environmental stimuli (Kim et al.,2012).

Resveratrol inhibits the p38 MAPK-cytosolic phospholipase A<sub>2</sub>-AA-TxA<sub>2</sub>-[Ca<sup>2+</sup>] cascade as well as NO/cyclic GMP activation. This, in turn, inhibits the activation of phospholipase C and/or PKC (Shen et al.,2007).

**Table 1. Biological activities of resveratrol**

<b>Role</b>	<b>Effect</b>	<b>Reference</b>
<b>Anti- diabetic effect</b>	Modulates glycemic control,improve insulin sensitivity and decrease HA1C.	<b>(Berman et al., 2017).</b>
<b>Anti- inflammatory effect</b>	Decreased expression of related factors including NF-KB, TNF- $\alpha$ , and IL-1 $\beta$ in the peripheral nerves.	<b>(Zheng et al., 2013).</b>
<b>Anti- oxidant effect</b>	Regulation of redox genes leading to $\downarrow\downarrow$ ROS production from NADPH oxidases. Also, an up-regulation of antioxidant enzymes by RV accelerates the detoxification of ROS.	<b>(Meng et al., 2020).</b>
<b>Anti- cancer effect</b>	Inhibits the AKT, MAPK, NF-B signaling pathways, and targets COXs. these actions reduce inflammation and prevent the development of cancer.	<b>(Rauf et al., 2018).</b>
<b>Anti- aging effect</b>	Increase SIRT1 , Klotho gene expression,activating AMPK, and Nrf1 signaling pathway.	<b>(Chen et al., 2021).</b>
<b>Cardioprotective effect</b>	Control eNOS ,improved the mechanical performance of the heart upon reperfusion , reduced myocardial cell death, and improve coronary artery disease	<b>(Najafi et al., 2021).</b>
<b>Anti- obesity effect</b>	$\uparrow\uparrow$ Mitochondrial respiration ,limitation of triacylglycerol accumulation and limit the responses of adipocyte to the insulin activation	<b>(Zhou et al., 2018).</b>
<b>Anti- hypertensive effect</b>	$\downarrow$ BP by vasodilatation, $\uparrow$ levels of NO andneovascularization	<b>(Cho et al., 2017).</b>
<b>Neurological effect</b>	Reduce MMP-9 and A $\beta$ s in the brain and improve the activities of AMPK and SIRT1	<b>(Zhang et al., 2021).</b>

**Abbreviations:**HA1C: Hemoglobin A1C, **TNF $\alpha$ :** Tumor necrotic factor  $\alpha$ , **IL1 $\beta$ :** Interleukin 1 $\beta$ , **NF-KB:**Nuclear factor kappa B, **ROS:** reactive oxygen species, **eNOS:** endothelial nitric oxide synthase, **Nrf:** nuclear factor E2-related, **SIRT1:**Sirtuin 1, **AMPK:**Mitogen-activated protein kinase, **BP:** blood pressure, **MMP-9:** matrix metalloproteinase , **NO:** nitric oxide.

#### 5.2.4. Activator protein-1 pathway

Activator protein-1 is transcription factor. Numerous cell functions, including apoptosis, inflammation, differentiation and proliferation, all are regulated by AP-1 (Eferl and Wagner,2003).

Resveratrol can prevent Phorbol 12-myristate 13-acetate or TNF from activating AP-1-mediated gene expression. Resveratrol has the ability to directly inhibit COX-2 activity, but it also appears to have a stronger indirect inhibitory effect by

reducing COX-2 expression after decreasing AP-1(Kundu andSurh,2004).

### 5.3. Antioxidant role

Oxidative stress is described as an imbalance between the antioxidant and oxidative systems in cells. Damage to tissues and cells occur due to response to oxidative stress, which is triggered when cells accumulate a burst of reactive oxygen species (ROS) that cannot be eliminated (Gorrini et al.,2013).Currently, it is known that oxidative stress plays an important role in the etiology of cardiovascular illnesses, diabetes and its complications (Odegaard et al.,2016).Resveratrol has been demonstrated to have anti-oxidant properties through a number of different mechanisms, including: scavenging free radicals, lowering the production of ROS, promoting the expression of antioxidant molecules through a number of signaling pathways, inducing autophagy and activating the production of endogenous antioxidant enzymes(Meng et al.,2020). Under oxidative stress, many ROS are generated, and these ROS have the power to deactivate a number of protective factors, including AMPK, SIRT6 and other signaling pathways, FOXO, PGC-1, and other protein factors.The body's antioxidant defense mechanism is significantly regulated by Nrf2, which can improve cells' response to oxidative damage (Volpe et al.,2018).It has been discovered that RV can mediate its antioxidant effects through downstream gene expression in the liver and elevating the protein level of Nrf2(Bagul et al.,2012).

### 5.4. Cardio protective Effects

Resveratrol has the ability to control endothelial nitric oxide synthase (e NOS), which decreases the expression of vasoconstricting molecules and enhances nitric oxide-mediated vasodilation (Najafi et al.,2021).

Additionally, RV was important for myocardial infarction size reduction and post-ischemic functional recovery (Dai et al.,2007). There is a strong evidence that RV can modify cardiomyocytes directly by prevent hypertrophy through reducing hemodynamic load(Dolinsky and Dyck,2011).The use of RV in coronary heart disease increases flow-related vasodilatation and it has been discovered that long-term RV therapy lowers blood pressure(Timmers et al.,2011).

### 5.5. Antihypertensive effect

Today, idiopathic hypertension accounts for around 90% of cases, the cause of which is still unknown. Untreated hypertension can lead to the development of a number of medical disorders, such as coronary heart disease, stroke, retinopathy, nephropathy and other eye problems (Kannel,2000). So. Hypertension considered as the most critical and cost-effective risk factor for premature mortality globally (World Health Organization,2009). Resveratrol can reduce BP by many mechanisms including anti-oxidative processes, vasodilation and neovascularization(Cho et al.,2017). The vasodilator effect of RV occurs via increase

expression of SIRT1 (Menzies et al., 2013). The increased endothelial NO additionally has an antihypertensive effect by raising the production of heme oxygenase-1 (HO-1), which is precursor to bilirubin (Stocker and Perrella, 2006). Resveratrol antioxidative methods include inhibiting the formation of ROS, activating p38 MAPK and NF- $\kappa$ B in vascular smooth muscle cells and phosphorylating Akt (one of protein kinases). RV may also regulate AT1 expression by activating SIRT.1 (Miyazaki et al., 2008) and increase neovascularization mechanisms via increase vascular endothelial growth factor and its receptors. Also, increase HO-1 synthesis and thoredoxin (antioxidant) secretion. So together improve myocardial angiogenesis functions and antioxidant effect (Cho et al., 2017).

### 5.6. Anti-aging effects

Apart from its many other health advantage, resveratrol has the capacity to delay aging. Resveratrol main function is to regulate the expression of miRNA, which either kills cells or delay the beginning of diseases including diabetes, cardiovascular disease and aging. By activating off SIRT1 molecules and sirtuins, RV can lengthen human life (McCubrey et al., 2017). RV was discovered to have anti-aging characteristics because it inhibits mitochondrial ATP synthase (Fiorillo et al., 2016). In addition to having negative effects on ageing, resveratrol will increase SIRT1 expression and decrease the generation of endogenous melatonin (Ramis et al., 2015).

According to reports, the Klotho gene has anti-aging properties. The increase of Klotho expression may be effective in age-related disorders (Chen et al., 2021). Resveratrol enhance the feeling in the kidneys of the activated transcription factor 3 and the anti-aging coagulation gene that interacts to modulate Klotho-mediated RV activation (Chen et al., 2021). Recently, RV has been discovered to have anti-aging characteristics because it inhibited mitochondrial ATP synthase (Ni et al., 2021).

### 5.7. Role in cancer prevention and treatment

Resveratrol can be as effective as the best complementary medicine for treating and stopping a variety of cancers, including those of the eyes, liver, cervix, kidneys, blood, breast, brain, bladder, prostate, ovaries, stomach, skin, esophagus, heads, lungs, thyroid, and neck because of its natural source, safe use and availability compared to other cancerous drugs (Fiorillo et al., 2016). RV inhibits the AKT, MAPK, and NF- $\kappa$ B signaling pathways, and targets COXs, which produce pro-inflammatory chemicals that encourage the formation of tumors. These actions would all reduce inflammation and prevent the development of cancer (Rauf et al., 2018).

Resveratrol activate the transcription factor Nrf2, which moves into the nucleus and activates the production of anti-oxidant genes. In certain cell lines, RV can increase apoptosis and slow the development of cancer cells. Resveratrol influences Nrf2 signaling and nutrient-deprivation



autophagy factor-1 (NAF-1) in pancreatic cancer, which makes cells more sensitive to gemcitabine (a deoxycytidine analogue that is frequently prescribed for chemotherapeutic treatment of different solid tumors and is regarded as the standard treatment for pancreatic cancer). Additionally, RV has been shown to reduce NAF-1 synthesis, which has anti-apoptotic effects and increase Nrf2 signaling (Kulkarni and Cantó, 2015).

Breast cancer is caused by catechol estrogen, which is carcinogen. Catechol estrogen can be metabolized by the enzyme UGT1A8. Through degradation of catechol estrogen and activation of the Nrf2 gene expression, RV can enhance the expression of UGT1A8. Additionally, Nrf2 controls the UGT1A8 gene promoter and activates the UGT1A8 gene in renal cell carcinoma. RV increases the expression of Nrf2 cells, which reduces the toxicity caused by ochratoxin, which induce oxidative stress, has nephrotoxin activity and causes renal dysfunction (Alavi et al., 2021).

### 5. 8. Anti-Obesity role

Resveratrol as a calorie-restriction inducer for the treatment of obesity. For 30 days, obese males taking 150 mg/day of RV lead to cellular and systemic indicators of metabolism, such as lower levels of blood sugar, triglycerides and elevated mitochondrial respiration in the muscle. RV reduces lipid buildup via reducing cellular survival and fat synthesis (Zhou et al., 2018).

When lipopolysaccharide(LPS) and protein down-regulation are coupled they activate pathways in the electron transport chain that cause inflammation. RV (100 mg/kg/day) reduces the effects of LPS and improves dysfunctional adipose tissue brought on by inflammatory stimuli, this lead to reduction of blood glucose levels, insulin resistance and reduces body weight including fat and weight (Le Duc et al., 2021).

### 5.9. Neurological role

Alzheimer's disease (AD) and stroke are neurological disorders brought by inflammatory damage and oxidative stress to the central nervous system. Resveratrol has potent anti-oxidative and an anti-inflammatory properties; many theories suggest that RV could be useful for treatment of neurological diseases. RV is also known to enhance the functions of SIRT1, AMPK, and PGC-1 (metabolic regulators which are involved in the beginning of neurological diseases) (Zhang et al., 2021).

Alzheimer's disease is characterized by progressive decline of cognitive and behavioral abilities and occurrence of AD is unknown, but onset and progression of disease occur by several biomarkers. Apolipoprotein E and the amyloid beta precursor protein promote the buildup of amyloid  $\beta$  - plaque (A $\beta$ ). Alzheimer's disease is also associated with elevated inflammation, oxidative damage and genetic changes (Pasinetti et al., 2015).

As RV affects a number of AD indicators, it is helpful for patients with mild to moderate AD. It was discovered that patients received RV for one year reduced MMP-9 levels (a matrix metalloproteinase that degrades components of the extracellular matrix, an activity that is prominent with AD neurodegeneration). Despite the fact that resveratrol was proved to be rapidly metabolized, RV and its metabolites were detected at high concentrations in the CSF, demonstrating its potential to penetrate the blood-brain barrier (Chung et al., 2010). The decrease in MMP-9 may suggest that resveratrol strengthens CNS by lowering permeability and preventing pro-inflammatory chemicals from penetrating the brain (Moussa et al., 2017). Additionally, people using RV had a slower decrease in CSF' levels of A $\beta$ 40 and A $\beta$ 42 indicating lower accumulation of A $\beta$ s in the brain. This result provided evidence that RV could be a safe and effective treatment for AD (Turner et al., 2015).

Brain stroke is a neurological condition responsible for the highest rates of mortality and morbidity worldwide. (Thordardottir et al., 2017). In brain ischemic stroke MMPs is important biomarkers. Currently, the only method of treating brain ischemia that is reliable and safe is recombinant tissue plasminogen activator (r-tPA) (Feigin et al., 2014). Though, it must be given within three hours after the onset of a stroke, as its therapeutic window is severely restricted. It has been demonstrated that delayed r-tPA therapy increases MMP expression. Resveratrol has

the capacity to lower MMP-9 levels, which reduces CNS permeability and reinforces the BBB. RV improved the therapeutic window of r-tPA, making the treatment for people suffering from brain ischemic stroke more effective (Saver, 2011).

## 6. Resveratrol adverse effects

### 6.1. Resveratrol metabolites can exhibit cytotoxic effects

Resveratrol's o-quinone metabolites have been linked to harmful effects, especially on the skin. Alkylation processes and oxidative stress play a role in these harmful effects (Chen et al., 2016). Hepatic and renal toxicity can potentially result from O-quinone-induced suppression of P450 oxidative enzymes or alkylation of specific proteins such Keap1 (Kelch-like ECH-associated protein 1), Nrf2, I kappa B kinase, and NF- $\kappa$ B. O-quinones may also decrease glutathione levels and interfere with the activity of nicotinamide adenine dinucleotide phosphate oxidase, which can induce oxidative stress (Bolton et al., 2018).

Rhododendrol, a tyrosinase inhibitor which is cosmetic ingredient used for whitening/lightening, may increase the frequency of leukoderma skin toxicity. Similar to rhododendrol, resveratrol is a p-substituted phenol that is quickly transformed into lethal o-quinones as shown in (Fig. 4), Bolton and Dunlap, 2017).

### 6.2. Resveratrol cytotoxic mechanisms can induce DNA breaks

Under specific conditions, an antioxidant may act as a pro-oxidant, causing DNA damage and accelerating lipid

peroxidation. In fact, depending on the dose, form, circumstances, timing, kind of cells employed and basal redox status, RV may actually exhibit pro-oxidant rather than antioxidant effects (Abe et al.,2016).

In vitro, RV functions as a pro-oxidant molecule that can inhibit DNA repair pathways, activate apoptotic and cytotoxic pathways and damage DNA (Zheng et al.,2018).The capacity of RE to cause DNA breaks has a potential therapeutic benefit that can be harnessed when RE is used against malignant cells(De

La Lastra and Villegas, 2007).Resveratrol also inhibits essential DNA synthesis enzymes like DNA polymerases and ribonucleotide reductase (Liu et al.,2017).Moreover, RV had been shown to produce DNA damage in colon cancer cells through activation of the ataxia-telangiectasia mutated kinase and topoisomerase II and to trigger p53-dependent apoptosis shown in (Fig.4) (Leon-Galicia et al., 2013).

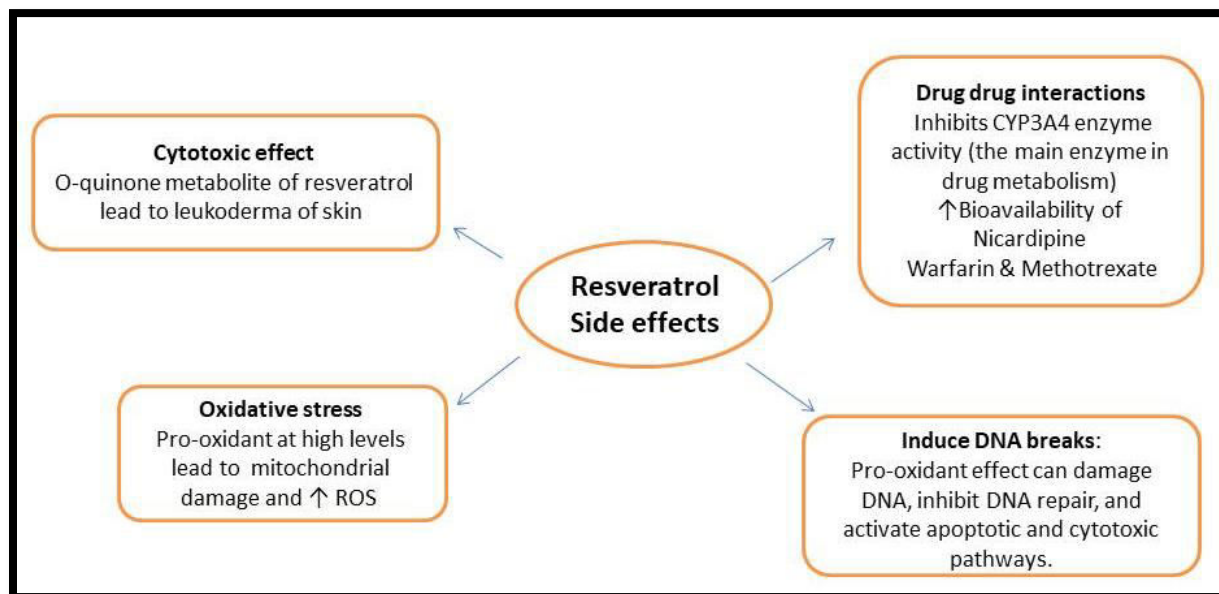


Fig.4. Resveratrol adverse effects.

### 6.3. Resveratrol cytotoxic mechanisms can induce oxidative stress

Resveratrol has biphasic concentration-dependent effects, an antioxidant or pro-oxidant. Numerous investigations showed that both in vivo and in vitro, RV is an antioxidant at low doses and pro-oxidant at high levels (Demoulin et al.,2015). It appears that RV pro-oxidant

effects are usually followed by apoptosis, downregulation and cellular damage. N-acetyl cysteine and diphenyleneiodonium have an interesting ability to block RV-induced pro-oxidant effects, suggesting a function for flavin oxidases in pro-oxidant RV-induced toxicity(Posadino et al., 2019).High-dosage-associated RV-elicited oxidative damage appears to be mediated via

mitochondrial damage caused by cytochrome P450 enzyme CYP2C9 as shown in (Fig. 4, (Posadino et al., 2015)

#### 6.4. Resveratrol interacts with and affects the action of other medications

Resveratrol indirectly interacts with other medicines, through inactivation or overexpression of CYP450 enzymes and drug transporters, the primary cellular system responsible for drug metabolism (Basheer et al., 2017). Over 50% of widely viable medications that rely on metabolic clearance are metabolized by the P450 enzyme CYP3A4, which is the primary enzyme in this process. Various studies indicate that RV modifies or inhibits the function of the CYP3A4 enzyme (Basheer et al., 2016).

Oral bioavailability of Nicardipine can be increased by RV therapy, and this was linked to a reduction in P-glycoprotein-mediated efflux because P-glycoprotein is a key drug transporter (Choi et al., 2009). Additionally, it was demonstrated (both *in vivo* and *in vitro*) that RV inhibited drug transporters like P-glycoprotein, multidrug resistance-associated protein 2, and organic anion transporters (OAT1/OAT3), these improve methotrexate absorption in the intestine and reducing methotrexate renal elimination. This RV impact induces liver toxicity (Jia et al., 2016). Warfarin's anticoagulant activity may be increased by RV, raising the possibility of bleeding (Chiba et al., 2016). Co-administration of resveratrol has also been shown to reduce the effects of a number of other medications. For example, reduce the impact of protease inhibitors for the human immunodeficiency virus (Symington et al.,

2017) and it can interact with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, anti-arrhythmic agents, calcium channel agonists, antihistamines and immunosuppressant drugs as shown in figure 4 (Stephan et al., 2017).

#### Conclusion

Our review article has focused in RV as nutraceutical and therapeutic agent. Resveratrol importance was derived from its biological activities including: anti-inflammatory, anti-oxidative, anti-carcinogenic, cardio protective, anti-aging, anti-diabetic, neuroprotective and so on. Recently, RV can be recommended as a therapeutic strategy for the treatment and prevention of a wide variety of chronic illness.

Although, most of the studies indicated the safety of RV; but, there are some reports related to its toxicity.

So, further researches needed to clarify the mechanism of action of RV, more detail to understand their metabolic pathways, human toxicity and bioavailability.

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