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Resveratrol: Biological Activities and Therapeutic Potential

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Abstract: Resveratrol is a polyphenolic flavonoid initially identified as a phytoalexin and as a major constituent of red wine. However interest in this molecule initially developed as a cardioprotective agent and in due course of time therapeutic actions came into limelight. This article explores the different therapeutic activities of Resveratrol and highlights their possible mode of action responsible for its therapeutic action. It becomes evident from this article that Resveratrol has a pharmacological agent that has widespread targets and therefore due emphasis on specific biological action need to be addressed using medicinal chemistry and quantitative structure activity relationships in developing new congeners of Resveratrol to be exploited as drugs.

Keywords: Resveratrol, phytoalexin, cardiotonic, anti-cancer, anti-oxidant, antimicrobial

1. INTRODUCTION

Resveratrol (RSV) or trans-3, 4, 5-trihydroxystilbene (Fig 1.) was originally identified as a phytoalexin that in nature protects plants against infection against fungi especially *Botrytis cinerea* (Langcake and Pryce, 1976). Resveratrol was identified as a phytochemical since 1940's when it was first isolated from white hellebore (*Veratrum grandiflorum O. Loes)* and later from the medicinal plant *Polygonum cupsidatum.* Resveratrol is found in at least 72 plant species (Dercks and Creasy, 1989) and is formed via a condensation reaction between 3 molecules of malonyl CoA and 1 molecule of 4-coumaroyl CoA (Soleas *et al*., 1997). Both of these plants find use in the Chinese as well as Japanese medicine. Resveratrol was initially identified as an inhibitor of enzymes involved in Arachidonate metabolism in the leukocytes and of partially purified kinases. Resveratrol is also present in peanuts, soys and other plant product;

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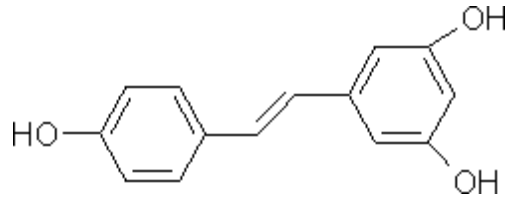

Figure 1: Structure of Resveratrol.

however the content is much less as compared to red wine where it can go up to 14mg L^{-1} depending upon the types of grapes used for the wine manufacture.

In spite of rather a fatty diet the French population has a lower incidence of cardiovascular diseases –i.e the French paradox has been attributed to uptake of resveratrol by red wine consumption which is a long standing component of their diet (Fremont, 2000). Thus this paradox has been the primary driver for impetus in research on resveratrol. Hence the present review focuses on the naturally occurring polyphenol, Resveratrol for its biological activities as well as therapeutic potential

2. HEALTH BENEFITS OF RESVERATROL

Incidentally the first use of grape extracts as medicine has been dated 2000 years ago as "darakchasava", a well-known Indian herbal preparation of which the main ingredient is *Vitis vinifera*L (Paul *et al*., 1999). This Ayruvedic medicine was prescribed as a cardiotonic. Today a number of therapeutic actions have been reported by Resveratrol viz. anti-carcinogenic, anti-inflammatory, anti-diabetic, anti-microbial, cardioprotective, neuroprotective, anti-ageing, anti-oxidant and anti-viral activities (Fig.2).

2.1 Resveratrol as Anti- carcinogenic/ Chemo preventiveagent

COX primarily catalyze the conversion of arachidonic acid into prostaglandins, a proinflammatory substance which can stimulate tumor cell growth and suppress immune surveillance (Plescia *et al*., 1975; Goodwin, 1984). COX can activate carcinogens to forms that damage genetic material (Zenser *et al*., 1983). During screening of plant extracts for their cyclooxygenase (COX) inhibitory potential for identification chemo-preventive agents, an extract of *Cassia quinquangulata* Rich. (Leguminosae), collected in Peru, was identified as a potent inhibitor wherein resveratrol was identified during the bioassay guided isolation. Resveratrol possesses cancer chemo-preventive and cytostatic properties via initiation, promotion and progression of carcinogenesis (Jang *et al*., 1997).

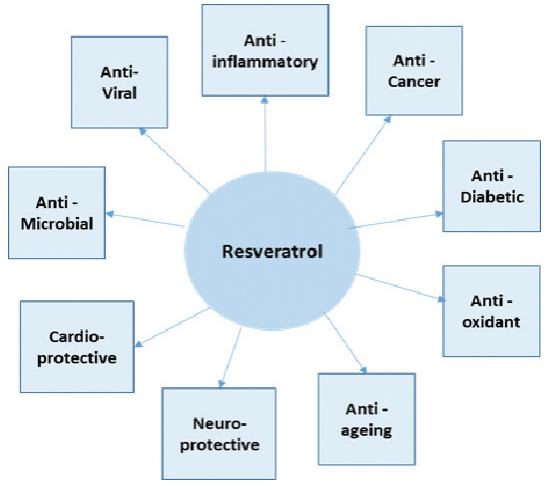

Figure 2: Biological activities of Resveratrol.

Resveratrol also suppresses the proliferation of variety of tumor cells, including lymphoid and myeloid cancers; breast, colon, pancreas, stomach, prostate, headand neck, ovary, liver, lung and cervical cancers; melanomaand muscles. It also induces apoptosis through the caspase-8-dependent pathway (receptor mediated) or the caspase-9-dependent pathway (mitochondrial), or both. Apoptotic and growth inhibitory effects of RSV were observed in human B-cell lines which were derived from chronic B-cell malignancies (Roman *et al*., 2002). Fas signaling-dependent apoptosis was triggered by resveratrol in HL-60 human leukemia cells (Clement *et al*., 1998). Anti-proliferative effects against breast cancer cell lines viz. MCF-7, MCF-10F and MDAMB-231 was exhibited by resveratrol which was independent of estrogen receptor status of the cells. Wolter *et al*. (2001) reported that resveratrol inhibited growth and proliferation of Caco-2 cells through apoptosis. Human pancreatic cancer cell lines PANC-1 and AsPC-1 were inhibited by resveratrol via apoptosis.

Proliferation of androgen dependent and androgen independent prostrate cells were suppressed by resveratrol. Thus resveratrol interacts with a variety of signaling molecules such as NF-κβ, Egr-1; inhibits protein kinases such as JNK, MAPK, Akt, PKC, PKD and casein kinase II and down-regulates the products of genes such as VEGF, IL-1, IL-6, IL-8, AR, 5-LOX and COX-2 while exerting the chemopreventive or anti-cancer action.

2.2 Resveratrol as a neuroprotective agent

Resveratrol has been reported to be effective in neuroprotective activity which is attributed to its anti-oxidant properties. It has been found effective against

ischemic brain injury and in kainic acid induced brain seizures or neuronal damage in rodents (Wang *et al*., 2002; Wang *et al*., 2004).

Resveratrol has an ability to delay the onset of neurodegradation due to the formation of β-amyloid plaque formation and oxidative stress. Alzheimer's dementia (AD) leads to progressive loss in the memory but the etiology of AD is completely unknown but formation of β-amyloid plaques have been found to be highly neurotoxic which occurs in AD. Oxidative stress serves as a precursor for the amyloid precursor protein formation leading to AD (Karuppagounder *et al*., 2009). Resveratrol supplementation has been found to diminish the plaque formation in rodent brain in a region specific manner as well as decreased the level of glutathione. Marambaud *et al*. (2005) exhibited that resveratrol *in vitro* removes the amyloid deposits by increased intracellular proteasomal activity. Resveratrol supplementation in rodents has also demonstrated the ability to prevent kainic acid induced brain seizures (Gupta *et al*., 2002).

Resveratrol has also been tested for its beneficial effects in 6-hydroxydopamine induced Parkinson's rat model. In this model 6-hydroxydopamine induced chronic inflammation, mitochondrial dysfunction, and oxidative stress, and loss of dopaminergic neurons in the substantia nigra. To overcome these effects Resveratrol significantly decreased the level of COX-2, TNF-α mRNA and COX-2 protein expression in the substantia nigra (Sun *et al*., 2010).

2.3 Resveratrol as an antiviral

Resveratrol exerts an antiviral action against potent DNA as well as RNA viruses (Campagna and Rivas, 2010). The very first virus in which resveratrol inhibited replication was HSV (Herpes Simplex Virus) 1 and 2 (Docherty *et al*., 1999). It blocks the viral DNA synthesis to inhibit the polyomavirus replication (Berardi, *et al.,* 2009). Apart from this resveratrol also exhibits anti-HIV activity, making it a strong lead compound for the development of new anti-HIV agents. Resveratrol in a dose dependent fashion also inhibits Epstein Barr Virus, Human cytomegalovirus and Varicella Zoster Virus (Docherty *et al*., 2006; Evers *et al*., 2004; Kapadia *et al*., 2002).

2.4 Resveratrol as an anti-inflammatory agent

The two primary enzymes involved in the synthesis of pro-inflammatory mediators are 5-HETE (5-hydroxy-6, 8, 11, 14-eicosatetranenoic acid), thromboxane A2, prostaglandins & HTT (12- hydroxyl-5, 8, 10 - heptadecatrienoic acid) are cyclooxygenase and lipoxygenase pathways (Cuendet and Pezzuto, 2000). The prostaglandins have been implicated in promoting cell proliferation, suppressing immune surveillance and stimulating

tumorigenesis (Gusman *et al*., 2001). Resveratrol has been found to inhibit 5- lipoxygenase product 5-HETE and COX products HHT and thromoboxane B2 (Kimura *et al*., 1985). The COX and LOX inhibitory activities of RSV also account for its protective effect against oxidative stress induced death of human erythroleukaemia K652 cells (MacCarrone *et al*., 1999). The anti-inflammatory activity has been demonstrated in a rat model of carrageenan induced paw edema (Gentilli *et al*., 2001). RSV remarkably inhibits the ROS production, release of elastase and β-glucuronidase from neutrophil granules and cell surface expression of the β2-integrin MAC-1 upon PMN stimulation indicating that RSV elicits an inhibitory action at all physiological phases of inflammatory response (Pervaiz, 2003). Resveratrol also has beneficial effect on the control of anti-inflammatory disorders such as arthritis and inflammatory bowel disease.

2.5 Resveratrol as an anti-diabetic

Diabetes mellitus is a modern day epidemic which is characterized by high blood sugar level which may be due to abnormal insulin secretion or insulin receptor or post receptor events affecting the overall metabolism of carbohydrates, fats and proteins. Resveratrol has been found to improve insulin action in different animal models (Sharma *et al*., 2011). The anti-hyperglycemic and anti-oxidant activity of resveratrol has been assessed by its modulatory effects on the activities of carbohydrate metabolizing enzymes in the kidney and in the hepatic tissues of streptozotocin-nicotinamide induced diabetic rats (Palsamy and Subramanian, 2009; Movahed *et al*., 2013).

Resveratrol administration also reduced the level of glycosylated hemoglobin (HbA_{1c}) as well as improved plasma insulin level by stimulating β-cells to synthesize more insulin and regulate HbA_{1c} formation rate thereby exhibiting an insulin mimetic effect (Su *et al*., 2006).

2.6 Resveratrol as an anti-oxidant

The consumption of oxygen in normal functions such as respiration and cell mediated immune functions leads to the production of Reactive Oxygen Species (ROS). ROS comprises of free radicals such as superoxide anion radicals ($O_2^{\cdot-}$), hydroxy radicals ($OH^{\cdot}$) and non-free radical species such as hydrogen peroxide (H_2O_2) and singlet oxygen (Gulcin *et al*., 2005). As ROS are continuously produced during the normal physiological functions of the cell they cause peroxidation of lipids in the membranes. They are also capable of damaging biomolecules like the nucleic acids, polyunsaturated fatty

acids, proteins, carbohydrates apart from damage to DNA. In case of failure to effectively scavenge ROS, several diseases are indicated due to damage to the biomolecules such as proteins, lipids and nucleic acids (Halliwelland Gutteridge, 1990). Anti-oxidants increasingly find applications in enhancing the shelf life and stability of food products and pharmaceuticals as they retard lipid peroxidation (Haliwell, 1997).

Resveratrol has exhibited to have a higher ABTS (2, 2- azinobis (3-ethylbenzthiazoline-6-sulfonic acid); DPPH (1, 1,-diphenyl-2-picrylhydrazyl) and hydroxyl scavenging activity when compared to propyl gallate, vitamin C, Vitamin E (Soraes*et al*., 2003). It also inhibits oxidation induced apoptosis in a variety of cell lines such as including Swiss 3T3 mouse fibroblasts, rat pheochromocytoma (PC12), human peripheral blood mononuclear (PBM), and human retinal pigment epithelium(RPE) cells (Jang and Surh 2001; Losa 2003; Kutuk*et al* 2004; King *et al*. 2005). Resveratrol has also been found to inhibit the inflammatory cytokines such as tumor necrosisfactor-α (TNF-α) and interleukin-1β (IL-1β) (Pendurthi*et al*., 1999; Culpitt*et al*., 2003).

2.6 Resveratrol as a cardioprotective agent

Cardiovascular disease are the leading causes of mortality throughout the world. The common risk factors for cardiovascular diseases are hypertension, obesity, dyslipidemia, insulin resistance, glucose intolerance and increased oxidative stress. A significant observation was the South French population despite high fat consumption in their diet and heavy use of tobacco products had a very low incidence of cardiovascular disease. This is referred to as French Paradox and may be associated with the dietary consumption of red wine which is a dietary source of resveratrol and may be associated with the positive cardiovascular effects of moderate wine consumption (Constant, 1997). It has been found that resveratrol inhibits LDL (low density lipoprotein) oxidation which is the key event in the initiation of atherosclerosis (Belguendouz *et al*., 1997; Zou *et al*., 1999; Zou *et al*., 2000).The second mechanism by which resveratrol acts as a cardioprotective agent is by inhibition of platelet aggregation (Wang *et al*., 2002). Platelet aggregation play a very important role in hemostasis bywhich injury in the vascular endothelium is rapidlyrepaired in order not to compromise the fluidity ofthe blood. Normally the platelets adhere to sub-endothelial matrix of damaged vessel then spread over the surface and form a thrombus by recruiting the additional platelets. Improper regulation or over activity of this repair system leads to pathological thrombosis. During the process of atherogenesis an essential requisite is migration and proliferation of smooth muscle cells in the intima of susceptible vessels. Resveratrol has

been found to suppress this proliferation of smooth muscle cells as well as pulmonary aortic endothelial cells (Zou et.al, 1999 (b); Poussier *et al*., 2005).

Resveratrol also possesses vasorelaxation properties. The vasorelaxation is mediated in endothelium-intact and endothelium independentaortic rings via nitric oxide (NO)-dependent and -independent mechanisms, respectively. Resveratrol relaxed the endothelium intact rat aortic rings constricted by phenylephrine and potassium chloride via NO release; however, there was no vasorelaxation effect with endothelium-independent rings (Orallo *et al*., 2002). The release of NO has also been suggested as a mechanism for the reduction of ischemia-reperfusion injury experienced by rat hearts after resveratrol treatments (Hung *et al*., 2000).

Apart from the above actions, resveratrol is associated with dose-dependent increase in the expression of tumor suppressor gene p53, heat shock protein HSP27, quinonereductase 1 and 2, and altered subcellular distribution of nitric oxide synthase and apoptosis inducing factor (Wang *et al*., 2006). All these results support that resveratrol acts as a cardioprotective agent by plethora of activities which interfere with the events leading to atherosclerosis and Coronary heart disease.

2.7 Phytoesterogenic activity of Resveratrol

Phytoestrogens are non- steroidal compounds which resemble estrogens as they bind to estrogen receptors resulting in transcription of estrogen responsive genes. Resveratrol is similar to synthetic estrogen diethylstilbestrol (DES) and may possess estrogenic activity. It is also proposed that this estrogenic activity of resveratrol provides cardio- protection as well as prevents the risk of estrogen dependent cancers.

Resveratrol has been found to inhibit advanced glycation end products (AGE'S) induced cellular events which are involved in a variety of vascular complications (Mizutani *et al*., 2000). MCF-7, human breast carcinoma cell line has been studied for understanding the estrogenic properties of resveratrol. Resveratrol stimulates the estrogen regulated progesterone receptor expression in MCF-7 (Ghem *et al*., 1997; Lu and Serrero, 1999; Bhat *et al*. 2001). Ghem *et al*., (1997) found that resveratrol exhibited a super agonist property by inducing a reporter gene activity 2- to 3- folds greater than estradiol. Both cis- and trans- resveratrol exhibited a super agonist activity in MVLN cells, an estrogen dependent cell line (Basly *et al*., 2000).

Estrogenic activity of resveratrol has also been implicated in prevention of bone loss in post-menopausal women. Resveratrol enhances the proliferation of oestoblastic ML3T3-E1 cells and induces alkaline phosphatase activity which plays a role in bone mineralization (Mizutani *et al*., 1998). Further resveratrol

treated ovariectomizedratshave been found to have greater femur bone length, epiphysis bone mineral density and bone calcium content than ovariectomized rats without resveratrol treatment (Liu *et al.* , 2005)

2.8 Anti-ageing activity of Resveratrol

Anti-ageing interventions essentially refer to both cosmetic maintenance of age through appropriate healthful appearance as well as stemming up the development of degenerative diseases optimizing in the brain as well as in other tissues to prolong life. A family of enzymes called Sirtuins specifically Sirtuin 1 (SIRT1) possesses anti-ageing action. Resveratrol has been found to activate SIRT1 and also exhibits the anti-oxidant effects.

Thus SIRT1 activation leads to modulation of a variety of proteins including peroxisome proliferator activated receptor co- activator-1 α, the FOXO family, protein kinase B, and NF$\kappa\beta$. SIRT belongs to histone deacetylases (HDAC's). During *in vitro* screening of SIRT1 activators, Resveratrol was identified as the most potent of all the 18 inducers who activity was tested during the assay (Baur and Sinclair, 2006; Balan *et al*., 2008). Resveratrol extends the life span in *Saccharomyces cerevisiae*, *Caenorhabditiselegans* (Tissenbaum and Guarente, 2001) and *Drosophila melanogaster* only of the genes of SIRT2 are present in these organisms. Resveratrol has shown to extend the lifespan of short lived fish by 59% concomitant with maintenance of learning and motor function (Valenzano and Cellerino, 2006; Terzibasi *et al*., 2007). Resveratrol has also been found to be an activator of human SIRT1 (Borra *et al*., 2005)

2.9 Anti-microbial activity of Resveratrol

Phytoalexins are low molecular weight compounds which exhibit biological activity against a range of plant as well as human pathogens (Jeandt *et al*., 2002; Mahady, 2006). Resveratrol was initially identified as a phytoalexin in *Vitis vinifera* (grapes) which has been subjected to intensive investigation because of multiple implications on human health. As resveratrol possesses anti-oxidant properties it is expected that it may also possess antimicrobial effects and may be used to prevent microbial infections. Resveratrol has been previously reported to possess anti-viral activity.

Resveratrol has been found to inhibit the growth of *Helicobacter pylori* which is responsible for duodenal ulcer disease, dyspepsia, peptic ulcer and gastric B cell lymphoma (Mahady and Pendland, 2000). Resveratrol also exhibited a MIC of 200mg/L against *Propionibacterium acnes* growth which is a gram positive, non-spore forming anaerobic bacillus associated with acne vulgaris (Docherty *et al*., 2007). Resveratrol has exhibited a potential inhibition against fungi especially dermatophytic fungi viz. *Trichophyton*

mentagrophytes, *Trichophyton tonsurans*, *Trichophyton rubrum* and *Epidermatophyton floccosum* in a range of 25-50 µg/ ml. Thus there is an ample scope of using resveratrol to combat dermatophytic fungal infections (Chan, 2002). Resveratrol thus possesses potential to be used as a natural antimicrobial for functional as well as therapeutic applications.

3. CONCLUDING REMARKS

The body of evidence presented here clearly highlights the potential of Resveratrol as a pharmacophore with wide spectrum of targets. However it is currently recommended as a Nutritional supplement and not medicine due to its multifarious actions. The pharmaceutical industries are much interested in development of target specific drugs from Resveratrol and therefore requires concerted research efforts in medicinal chemistry and quantitative structural activity relationship to develop congeners of resveratrol which would work for a specific or targeted activity with least side effects.

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