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Chemotherapeutic Properties of Naturally Occurring Stilbene Polyphenol-*Resveratrol*

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Abstract: ***Stilbenes are low molecular weight polyphenols found in many plant species as plant antibiotics and produced in response to infection or stress as plant protectants. Many naturally occurring stilbene compounds like resveratrol (3,5,4' trihydroxystilbene) has multi-functional effects such as antioxidant, anti-inflammatory, anti-cancer, and cardio-protectant and recent studies focused on its positive effect on age related infertility problems. It increases vasorelaxation, lowers cholesterol, improves RBC deformability, activates potassium channels, positive effect on myocardial remodeling and inhibits platelet aggregation. Res involves in the prevention and treatment of autoimmune diseases by elevating proteoglycan level. Resveratrol activates anti-aging genes and extends life span in lower organisms. It is also known to exert nueroprotective property. This review article mainly focused on the therapeutic properties of stilbenes, such as resveratrol.***

Keywords: resveratrol, anti-inflammatory, anticancer, nueroprotective, antioxidant

1. Introduction

Stilbenes are secondary metabolites produced by plant families, the Pinaceae, Fabaceae, Cyperaceae, Betulaceae, Vitaceae, Polygonaceae, Dipterocarpaceae, Gnetaceae, Leguminoseae, and Poaceae [1], [2]. Stilbenes (1, 2-diphenylehtylene) are low molecular weight phytoalexins. The stilbene nucleus is based on a 14-carbon skeleton composed of two phenyl rings linked by an ethylene bridge. Stilbenes are derived from the general phenylpropanoid pathway starting from phenylalanine. There are two isomeric forms of stilbene: (E)-stilbene (trans-stilbene) which is not sterically hindered, and (Z)-stilbene (cis-stilbene) which is sterically hindered and therefore less stable. stilbenes are produced in response to fungal infection, injury, stress, and ultraviolet radiation. Stilbenes are appearing to have special function as protectants against various pathogens and abiotic stress within the plant defense system [3]. A series of trans-stilbene derivatives have been evaluated for their antimicrobial, antioxidant and anticancer potentials [4]. Stilbene derivatives are also widely used as fluorescent brighteners to create intense and bright shades when incorporate in plastic, textiles, pulp and paper industry [5]. Resveratrol was first identified in the roots of roots of white hellebore (Veratrum grandiflorum O. Loes), in 1940 [6] and later in the dried roots of Polygonum cuspidatum. Chinese and Japanese were using this as traditional medicine to treat suppurative dermatitis, gonorrhea favus, athlete's foot (tinea pedis), and hyperlipemia [7], [8]. The chemopreventive effects of resveratrol were first reported in 1997 by Jang et al and demonstrated its cancer chemopreventive property [9]. Its low bioavailability and early clearance [10] kept open door to modify its structure or synthesis of analogues.

2. Therapeutic Applications

Antioxidants

Cellular respiration generates lot of reactive oxygen species (ROS), including superoxide anion, hydroxyl radical, peroxyl radicals, and singlet oxygen. These molecules play a dual role as both beneficial and deleterious. At low or moderate level involve in cell responses to noxia, defense mechanism, participate in number cell signaling pathways. Overproduction of ROS results oxidative stress which leads the progressive oxidative damage to cell structures, membranes, proteins and nucleic acids. Therefore, ROS are the major causative agents of aging and number of pathological conditions in human beings such as cancer, stroke, heart diseases, multiple sclerosis, autoimmune disorders, pulmonary dysfunction and Parkinson's disease. ROS are the major causative agents of cancer as these molecules have the ability to attack base of DNA. Antioxidants are substances that slow down or prevent the oxidation of reactive oxygen species by donating one or more electrons. The unstable free radicals that contain one or more unpaired electrons receive electrons form antioxidants and stabilize. Stilbene derivatives have attracted the world because of its biological applications and structural diversity. They are the promising therapeutic antioxidant agents. The risk of coronary heart disease and myocardial infarction are strongly related to oxidation of low-density lipoprotein (LDL) molecules [11]. An in vitro study of resveratrol shows prevention of LDL oxidation by chelating copper and also by directly scavenging free radicals [12].

Resveratrol is natural antioxidant neutralizes or scavenges by different mechanisms such as (i) competition with coenzyme Q and decrease the oxidative chain complex and prevent ROS generation, (ii) scavenging $O_2^{\circ-}$ radicals formed in the mitochondria and (iii) inhibition of lipid peroxidation

[13]-[15]. low concentrations of resveratrol inhibit the H_2O_2 induced caspase activation and DNA fragmentation in human leukemia cells through pro-oxidant effect [16]. Resveratrol is more powerful antioxidant than vitamin E in preventing LDL oxidation [17].

Anticancer Activity

Cancer is the undoubtedly stands front in the death stall, research is vigorous in cancer biology like diagnosis, treatment and prevention. One promising natural stilbene, resveratrol created the faith as anticancer drug molecule since last fifteen years. Resveratrol causes apoptosis of human tumors such as leukemia, colon, breast, prostate, and esophageal cells cell lines, by arresting at the S/G2 phase transition of the cell cycle. Resveratrol was also identified as an effective inhibitor of ribonucleotide reductase that catalyzes the rate-limiting step of de novo DNA synthesis [18]. Studies demonstrated that resveratrol induces apoptosis in cancer cells by blocking anti-apoptotic protein expression and inhibits the signal transduction through the phosphoinositide 3-kinase (PI_3K), mitogen-activated protein kinase (MAPK) or NF-B pathways. Ethanol extract from the stem bark of Vateria indica of vaticanol C, a resveratrol tetramer, demonstrated strong cytotoxicity against various tumor cell lines (mouse sarcoma 180 cells) and doesn't show any toxicity for the dose of 1000mg/kg body weight for period of 28 days cycle in mice models [19]. Resveratrol exerts antiproliferative and proapoptotic effects in human cancer cells at all stages of carcinogenesis that initiation, promotion and progression [20]. Studies suggest that the resveratrol analog 3, 5,2',4'-tetramethoxy-trans-stilbene is a more potent inhibitor of the growth of cancer cells compared to resveratrol [21].

According to National Breast Cancer Foundation, Breast cancer is the most commonly diagnosed cancer and second leading cause of death among women. One in eight women will be diagnosed with breast cancer in their lifetime. Large number of research articles demonstrated and have investigated the effects of resveratrol on breast cancer cells [22]-[32]. Early studies showed that resveratrol had significant growth inhibiting (antiproliferative) effects against breast cancer cell lines MCF-7, MCF-10F, and MDA-MB- 231, and these effects were estrogen receptor (ER) independent of the status of the cells [22]. Resveratrol inhibits estradiol induced cell proliferation in MCF- 7 breast cancer cell lines by inducing antagonistic effect on estradiol [23]. Resveratrol also inhibits ER negative human breast carcinoma cell line, MDA-MB proliferation by modulating the growth factor (TGF) and insulin-like growth factor I receptor mRNA [23].

Skin cancer is one of the most common types of human malignancy falls under two groups, melanoma and non-melanoma. World cancer report estimates 30% of newly diagnosed are skin cancers, 90% of them are due to exposure to UVB radiations. Many studies have demonstrated on the biological effect of resveratrol on both types. Moammir Hasan Aziz et al demonstrated for the first time that resveratrol inhibition of surviving-phosphoryalation at Thr34, results the decrease in survivin. survivin upregualtes the Smac/DIABLO and leads the apoptotic death of UVB induced malignant cells [33]. Jang *et al* assayed the chemopreventive effects of resveratrol on skin tumerogenesis SKH-1 hairless mouse model11 by tropical application of resveratrol and showed significantly inhibited tumor incidence and delayed the onset of new tumor. Similarly positive results were observed using a two stage, DMBA-initiated and TPA promoted murine skin cancer models [34]. One more study demonstrated that DMBA-induced mammary tumorigenesis was inhibited by purple grape juice extract in rats [35].

Current diet and lifestyle plays considerable role in the development of colorectal cancers. Appropriate nutrition and regular exercise can prevent colon cancer. Colorectal cancer is one of the leading causes of cancer deaths in the Western world. Jairam Vanamala et al observed suppression of cell proliferation in HT-29 and SW-480 colon cancer cells with 50-150μM resveratrol even the cells are primed to proliferate with IGF-1 by inhibiting the IGF-1R/Akt and Wnt/β-catenin signaling pathway proteins [36]. Resveratrol (30 mg/kg/d) has a therapeutic effect on HBx-induced fatty liver and the early stages of liver damage [37]. The transcription factor nuclear factor kB (NF-kB) plays major role in inflammatory diseases and oncogenesis. Resveratrol is the potent inhibitor of both NF-kB activation and NF-kB dependent gene expression and this leads to reduce mortality of from coronary heart disease and certain cancers [38].

Anti-inflammation

Some investigators have reported the potential neuroprotective activity for resveratrol based on several brain damage models. Similarly, several studies have shown resveratrol as a beneficial agent in the prevention/control of inflammatory disorders such as arthritis and inflammatory bowel disease [39]-[41]. Resveratrol control inflammatory disease by different mechanisms like; inhibition of synthesis and release of pro-inflammatory mediators, inhibition of inflammatory enzymes by modulating the cell signal pathways, inhibition of activated immune cell activity and modification of eicosanoid synthesis [39],[42]. Resveratrol also suppresses the activity of macrophages, T cells and B cell which were shown major role in inflammation [43]. Inflammation, which is beneficial with regard to the elimination of infectious organisms but always, has the potential of causing tissue damage and becoming noxious to the host. Inflammation is key factor in the initiation and pro-gression of atherosclerosis, which may cause major cardiovascular adverse events. Resveratrol not only modulates biochemical responses of polymorphonuclear leukocytes by interfering with the release of inflammatory mediators (e.g., platelet endothelial cell adhesion molecule-1) [44], but also suppresses the activity of T cells, B cells, and macrophages, which was shown by significant inhibition of their proliferation, antibody production, and lymphokine secretion [45].

Cardio Protective

Leading cause of death in world is cardiovascular disease. Cardiovascular disease caused due to hypertension, obesity, oxidative stress, etc. High intake of saturated fats are positively related to high coronary heart disease (CHD) and

most of the countries are prone to CHD but France is paradoxical in that eventhough they intake high saturated fats have mortality from CHD. This paradox is called as 'French paradox' because they consume more red wine [44]. Red wine contains stilbenes which protect them from severe CHD by Inhibition of platelet reactivity. Generally high density lipoproteins (HDL) are present in wine drinkers than non drinkers [46]. High HDL levels are known to have a protective effect against coronary vascular events due to atherosclerosis [47]. Corder R reported resveratrol mediated suppression of transcription of the ET-1 gene by inhibiting endothelin1 synthesis in cultured bovine aortic endothelial cells [48]. Over production of ET-1, the vasoconstrictor peptide causes vascular disease and atherosclerosis. K. Magyar et al. conducted clinical trials on 40 post-infarction Caucasian patients by administering resveratrol 10mg/day for the period of three months. Resveratrol found to have multiple beneficial effects such as FMD improved, enhanced red blood cell deformability, platelet aggregation was inhibited, LDL cholesterol level was decreased and improved left ventricular diastolic function [49]- [51]. Inappropriate or excessive aggregation of platelets leads to formation of thrombus and blockages in blood vessels which results in transient ischaemia, myocardial infarction or stroke. RBC deformability plays important role in coronary microcirculation because the average capillary diameter is less than the diameter of RBC. Many observations shown that resveratrol lowered down total cholesterol and increased HDL which reduced the formation of atherosclerotic plaques [52], [53]. Resveratrol possesses duel property as angiogenic and anti-angiogenic. It can prevent cardiac remodeling and promote cardiac regeneration. Less is known about its duel effects. Additional information is available from many research articles that lower doses of resveratrol enhanced proliferation and survival of cardiomyocytes and higher dose depressed cardiac function and also inhibited proliferation. High dose inhibits endothelial cell growth, thus preventing tumor growth [54]-[60]. Human experiments not showed any serious side effects with resveratrol [61]-[64]. In vivo studies of resveratrol in hypertensive diabetic rat show cardiovascular protection [65].

Resveratrol and ageing;

The ends of the chromosome are called telomeres provide stability for chromosomes. The results of research suggest that telomeres also participate in limiting cell division and play important roles in aging and cancer. Sirtuins are proteins of NAD+ dependent deacetylases family, presence of additional copies sir2 (silent information regulator 2) gene copies in saccharomyces cerevisiae shown extended lifespan [66]–[69]. Mammals have seven sirtuins, sirt1–7 in that sirt1 is similar to the Sir2 of *S. cerevisiae* based on amino acid composition. Sir1 knockout mice show developmental defects and lower lifespan. It is postulated that sirtuins proteins are important enzymes of stress resistance and promote lifespan. Resveratrol was shown Sir 2 dependent effect to extend lifespan of short lived fish upto 59% [70]. Non fluorescence assays confirm the activation of sirt 1 by resveratrol by A. Sauve et al.

Antimicrobial Activity

Resveratrol inhibits herpes simplex virus replication in Vero cell lines [71]. Resveratrol show positive effect in the treatment of *Helicobacter pylori* infections. antimicrobial assays proves its activity against pathogenic strains of *Candida albicans*, *Staphylococcus aureus* and *Escherichia coli* [72], *S. cerevisiae*, *B. cinerea*, *A. niger*, *S. cerevisiae* [73], *Salmonella enteric*[74], *Mycobacterium smegmatis* [75], *Propionibacterium acnes* [76]. Resveratrol inhibits replication of human cytomegalovirus [77], inhibits the lytic cycle of Epstein Barr Virus [78], protects from norovirus mediated acute gastroenteritis [79]. Bis resveratrol and transformed resveratrol show more antimicrobial activity [80]. Resveratrol also inhibits the adherence to human colonic cells by *Listeria monocytogenes* and *E. coli* [81]. The combination of stilbenes and fluconazole shows significant synergistic antifungal activity against *C. albicans* and low cytotoxicity against normal human cell lines [82].

Other therapeutic applications of Resveratrol

Resveratrol is also reported to act as an analgesic apart from many therapeutic applications [83]- [85]. It also show the protective activity against hearing loss [86] and show lipopolysaccharide induced anoxeric effect in rats [87]. Resveratrol reported to have positive effect in healing of kidney injury [88], [89], spinal card injury [90], [91], lung injury [92] and liver injury [93]. Many studies reported the evidence of resveratrol mediated healing of intestine and colon injury [94], [95]. Many studies highlighted the role of resveratrol in protecting brain damage and cerebral ischaemia [96]. Increase in amyloid plaques and amyloid polypeptide fibrils cause number of diseases like type II diabetes mellitus, Alzheimer's, Parkinson's, diseases of prion. Rajesh Mishra et al study showed that resveratrol inhibits the formation of amyloid polypeptide fibrils and facilitate the treatment of these diseases [97], [98]. Williams et al. did toxicity model study in rabbits and rats with low and high doses (750mg/kg/day) of resveratrol for three months. In models resveratrol were tolerated and showed no toxicity on their reproduction and even no adverse effect on developing embryo [99], [100]. UV-A induces the production of ROS which cause oxidative damage to retinal pigment epithelial, which leads the age related diseases and severe vision problems in aged persons[101]-[103]. Resveratrol protect from UV- A induced oxidative stress in RPE cells [104]. Liu et al. investigated through their study that the improved fertility in resveratrol treated aged mice. The treated old mice produced more quality oocytes than control [105], [106]. In another study resveratrol enhances the cytotoxicity of cisplatin commonly used drug for many solid tumors and protect against cisplatin induced nephrotoxicity in albino mice [107]. Its antidepressant activity was reported in studies of male wistar rat by Bouhali Imed Eddine et al [108]. This natural molecule can be viewed as best nutraceutical and multifunctional drug.

3. Conclusion

Prevention of cancer either by chemopreventive strategies based on naturally occurring agents or synthesized molecules or surgery, are most cost effective and socio-

economical issues. In India large group of people are not in the state of affordability or access to current treatment strategies. Naturally occurring phytochemicals have shown promising chemopreventive effects but the extensive clinical studies have not conducted and don't have long clinical history of many compounds. Therefore, more studies are needed for resveratrol and its derivatives as potential anticancer agents. More pharmacokinetics studies are needed to formulate dosage and specific target/site. Extensive pre- clinical studies and research is required to use of adjuvents, augments with stilbenes or its derivatives in high-risk populations of cancer of specific organs or sites. Based on current evidence of fruit or plant extracts and few synthesized stilbene derivatives are showing promising potential chemopreventive agents of cancer with low risk. Resveratrol can prevent or delay the onset of cancer, heart disease, ischaemic, and chemically induced injuries, diabetes, pathological inflammation and viral infection. Love your surroundings and have glass of red wine daily for good health.

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