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EFFECTS OF RESVERATROL AS AN ANTICANCER AGENT - A SYSTEMATIC REVIEW.

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ABSTRACT

The objective of the review was to analyse the chemopreventive and chemotherapeutic effects of resveratrol in various types of cancers along with its possible mechanisms. Literature search in Pubmed, Ebsco and Google Scholar was done for articles on role of resveratrol in various types of carcinomas using the search terms resveratrol and cancer, anticancer agents. *In vivo* and *in vitro* human as well as animal studies were searched from year 2009 till date. We also searched the reference list of various articles for additional papers. Systematic analysis of these articles was done to look for the cancer preventive and protective actions of resveratrol and the mechanisms by which it exerts its anticancer effects. Resveratrol has shown significant chemotherapeutic and chemopreventive effects in various carcinomas by its antioxidant, anti-inflammatory effects and also interferes with initiation, promotion and progression stages of carcinogenesis in various cancer cells Resveratrol can be used as an adjuvant to other chemotherapeutic agents in various carcinomas. But it needs more clinical trials to establish its efficacy and safety as an anticancer agent in humans.

KEYWORDS – **Resveratrol, Anticancer, Apoptosis, Cell Proliferation, Antiangiogenic**

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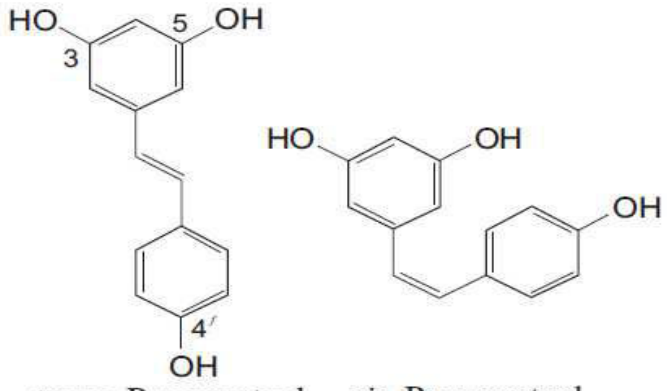
INTRODUCTION

Cancer is one of the leading causes of death worldwide. Approximately 13% of all deaths were caused by cancers in 2008.[1] Out of all the cancers, breast carcinoma is the second most common cancer accounting for about 1.38 million (~11% of all cancers) new cases and 6.0% mortality among all cancer related deaths in 2008. Similarly, colorectal carcinoma also puts significant burden on the health care system with many years of healthy life being lost, with 1.23 million new cases and 458,000 deaths (6.0% of all the cancer deaths) in 2008. Other carcinomas which contribute significantly to the disease burden include prostate carcinoma, leukaemia and skin cancers.[1]Various cancer chemotherapeutic drugs are available for treatment of different types of cancers but these drugs produce number of side effects owing to their narrow margin of safety. Thus now a days, alternative agents are being tried which are having efficacy against cancers but with less side effects.[2] Resveratrol is one such agent which recently has been extensively researched for its anti-cancer properties besides its other biological properties such as anti-diabetic, anti-platelet, cardioprotective, neuroprotective, anti-aging, antioxidant and anti-inflammatory.[3] Resveratrol (3,5,4'-trihydroxystilbene) is a natural polyphenolic, non-flavonoid antioxidant, is a phytoalexin produced by a wide variety of plants, such as grapes (Vitisvinifera), peanuts (Arachis hypogea)and mulberries in response to stress, injury, ultraviolet (UV) irradiation, and fungal (e.g., Botrytis cinerea) infection and also found in red wine.[4] It belongs to the stilbene family, a group of compounds having 2 aromatic rings joined by a methylene bridge and exists in two isomers: *trans*- and *cis*-resveratrol.[3]



Chemical Structures of Isomers of Resveratrol.

Various *in vivo* and *in vitro* human and animal studies have shown resveratrol to possess anticancer activity by modulating multiple pathways involved in inflammation, oxidation and by interfering at the initiation, promotion and progression stages of carcinogenesis in various cancer cells.

PHARMACOKINETICS

Effect of resveratrol has been studied over wide dose range of 5-500 mg/kg/day in humans without any significant adverse effects.[5] Recently it has been shown that resveratrol is metabolized to resveratrol sulfate but cells reuptake resveratrol sulfate and release the resveratrol for biological effect.[6] This may be the reason for the long term biological effect exerted by the resveratrol even though it has a half-life of ~2.5hrs.[5]

OBJECTIVE

The objective of the review was to analyse the chemopreventive and chemotherapeutic effects of resveratrol in various types of cancers along with its possible mechanisms.

MATERIALS AND METHODS

Literature search on Pubmed, Ebsco and Google Scholar was done for articles on the role of resveratrol in various types of

carcinomas. *In vivo* and *in vitro* human as well as animal studies were searched from year 2009 till date. We also searched the reference list of various articles for additional papers. Systematic analysis of these articles was done to look for the cancer preventive and protective actions of resveratrol and the mechanisms by which it exerts its anticancer effects.

RESULTS

The various mechanisms of action of resveratrol in different type of cancers are tabulated below.

Table 1
Resveratrol in Colorectal Carcinomas

S. No.	Reference	Type of Study	Model	Mechanism of Action/ Outcome
1	Ketan R Patel et al[7] (2010)	Human study (In vivo)	Histologically confirmed colorectal cancer patients	Resveratrol showed chemopreventive action in colorectal carcinoma by decreasing tumor cell proliferation
2	Anthony V Nguyen et al[8] (2009)	Human study (In vivo)	Colorectal cancer patients	Had colon cancer preventive activity by Suppressing Wnt pathway target genes (myc, jun, TCF-7, axin II, Cyclin D1) expression in normal colonic mucosa
3	Xiangli Cui et al[9] (2010)	Animal study (In vivo)	Dextran sulfate sodium (DSS) mouse model of colitis, Azoxymethane/DSS induced colon cancer model	Exhibited chemopreventive property by decreasing markers of inflammation, inhibiting neutrophil infiltration in mesenteric lymph nodes, lamina propria and modulating $CD3^+$ T cells that express TNF-α, IFN-γ
4	Francisca M. Santandreu et al[10] (2011)	In vitro	HT-29, SW-620 colorectal carcinoma cell lines	Potentiated the growth inhibition by antitumor drug 5-FU by increasing the oxidative stress produced by 5-FU. Resveratrol increased the intracellular levels of ROS and lipid peroxides, inhibited the expression of Akt and STAT3 proteins having oncogenic potential in colorectal carcinoma
5	M A Fouad et al[11] (2013)	In vitro	HCT116 and CaCo-2 human colorectal cancer cell lines	Exhibited cytotoxic, apoptotic and antiangiogenic effects by decreasing glycolytic enzymes, increasing citrate synthase activity, down regulation of VEGF, leptin and c-myc expression thus had promising anticancer activity.
6	Jairam Vanamala et al[12] (2010)	In vitro	HT-29, SW480 Human colon cancer cell lines	Suppressed colon cancer cell proliferation by increasing apoptosis even in presence of IGF-1. Suppressed IGF-1R/Akt/Wnt signaling pathways and activated p53
7	Chen J et al[13] (2009)	In vitro	Human colon cancer 1s174t cells & subcutaneously transplanted tumor in nude mice	Decreased expression of antiapoptotic factor bcl-2, increased expression of apoptotic factor bax and blocked the cell cycle at S phase thus inhibiting the growth of 1s174t cells

TNF-α, Tumour necrosis factor-α; IFN-γ, Interferon- γ; 5-FU, 5-Flurouracil; ROS, Reactive oxygen species; VEGF, Vascular endothelial growth factor; IGF-1, Insulin like growth factor-1

Table 2
Resveratrol in Breast Carcinoma

S. No.	Reference	Type of study	Model	Mechanism of action/ Outcome
1	Weizhu Zhu et al[14] (2012)	Human study (In vivo)	Adult women with increased risk of Breast carcinoma	Decreased methylation of tumor suppressor gene RASSF-1α and cancer promoting prostaglandin (PGE_2) leading to prevention of disease progression
2	Andreas J. Papoutsis et al[15] (2010)	In vitro	MCF-7 breast cancer cells	Antagonized the recruitment of AhR to the BRCA-1 promoter and also antagonized reduction of BRCA-1 expression in mammary epithelial cells Thus, prevented epigenetic silencing of BRCA-1 gene by AhR
3	Leon Galicia I et al[16] (2013)	In vitro	Breast cancer cell line MCF-7	Inhibited several genes of mismatch repair, DNA replication, homologous recombination and cell cycle Sensitized cancer cells to cell death in combination with anticancer drugs reducing toxicity and overcome chemoresistance

AhR, Aromatic hydrocarbon receptor

Table 3
Resveratrol in Haematological Malignancies

S. No.	Reference	Type of Study	Model	Mechanism of Action/ Outcome
1	Monika Podhorecka et al[17] (2011)	Human study (ex vivo)	Peripheral blood and BM mononuclear cells of untreated Chronic Lymphocytic Leukemia patients	Induced apoptosis in CLL cells alone as well as in combination with purine analogues Fludarabine and Cladribine by inducing DNA damage, decreased Bcl-2/Bax ratio, upregulation of p53 and p21, induction of NO, inhibiting COX
2	Aysun Adan Gokbulut et al[18] (2013)	In vitro	232B4 human Chronic Lymphocytic Leukemia cells	Decreased proliferation of human 232B4 CLL cells by inducing cell cycle arrest at G_0-G_1 phase, Inhibiting cell cycle progression. Induced apoptosis by increasing caspase-3 activity
3	Zeynep Cakir et al[19] (2011)	In vitro	Human HL60 Acute promyelocytic Leukemia cells	Had cytotoxic and apoptotic effects through increased accumulation of ceramides by induction of LASS genes (ceramide synthase gene) and repression of SK-1 and GCS genes (ceramide clearance genes)
4	MelisKartal et al[20] (2011)	In vitro	Human K562 Chronic Myeloid Leukemia cells	Increased intracellular generation and accumulation of apoptotic ceramide by decreased expression of SK-1 and GCS genes and increased LASS gene expression leading to cytotoxic and apoptotic effect of resveratrol

NO, Nitric Oxide; COX, Cyclooxygenase; ROS, Reactive Oxygen Species; GCS, Glucosyl ceramide synthase; SK-1, Sphingosine kinase-1; LASS, Longevity assurance gene

Table 4
Resveratrol in Skin Tumours

S. No.	Reference	Type of study	Model	Mechanism of Action/ Outcome
1	Jasmine George et al[21] (2011)	Animal study (In vivo)	Male, Balb/c mice	Decreased cell proliferation and induced apoptosis of skin tumor cells via decreased expression of phosphorylated MAPK family proteins, increased total p53phospho/p3 Combination of resveratrol and black tea polyphenol was more beneficial against cancer than either agent alone
2	Kim K H et al[22] (2011)	Animal study (In vivo)	Mice model (p53+/-/SKH-1)	Markedly delayed UV induced skin tumorigenesis and decreased malignant conversion of benign papillomas to SCC through decreased expression of TGF-β2 in UV induced SCC which leads to inhibition of TGF-β2/smad dependent and independent pathways, also increased level of epithelial cadherin. Suppressed the invasiveness of A431 cells
3	Bhattacharya S. et al[23] (2011)	In vivo animal study and In vitro study	Mouse model B16F10 and B16BL6 melanoma cells	Decreased tumor growth and metastasis by down regulating Akt in B16F10 and B16BL6 melanoma cells, inhibited migratory and invasive properties of these malignant cells Thus, Resveratrol reduced the malignant properties of highly invasive melanoma cells
4	AlpnaTyagiet al[24] (2011)	In vitro In vivo animal study	Head & neck SCC cells FaDu, Cal27, Det562 FaDuxenograft growth in nude mice	Decreased viability of FaDu, cal27 cells with no effect on viability of Det562 cells through its anti-proliferative, DNA damaging and apoptotic effects independent of smad4 status both in vitro as well as in vivo
5	Hao Y et al[25] (2013)	In vivo animal study	Human cutaneous SCC A431 xenografts in nude mice	Increased the apoptosis of human skin SCC A431 xenografts by upgrading the proteins and mRNA expression of p53, downgrading the proteins and mRNA expression of SVV

MAPK, Mitogen activated protein kinase; SCC, Squamous cell carcinoma; TGF-β_2, Transforming growth factor- β_2; Akt, Protein kinase B; SVV, Survivin

Table 5
Resveratrol in Prostate Cancer

S. No.	Reference	Type of Study	Model	Mechanism of action/ Outcome
1	Sandeep Sheth et al[26] (2012)	In vitro In vivo animal study	Human prostate carcinoma PC-3M-MM2 cells, DU145 &LNCaP cell lines S/C injection of these cells in flank region of 4 week old severely combined immunodeficient male mice	Decreased cell viability of tumor cell lines by decreasing expression of miRNA-21, decreased invasiveness of both androgen dependent and independent prostate cancer cells, decreased incidence of lung metastasis
2	Yu Wang et al[27] (2010)	In vitro	Prostate cancer cells androgen dependent LNCaP cells & androgen independent C4-2 cells	Inhibited growth of both androgen dependent and independent prostate cancer cells by acting as a weak estrogen, induced PTEN transcription by AR inhibition in prostate cancer cells

Table 6
Resveratrol in Nasopharyngeal Carcinoma

S. No.	Reference	Type of study	Model	Mechanism of Action/ Outcome
1	Meihond Zhang et al[28] (2013)	In vitro	Poorly differentiated human NPC cell line (CNE-2Z) Well differentiated human NPC cell line (CNE-1)	Decreased proliferation rate and induced apoptosis of both types of NPC cells by blocking PI3K/Akt signaling pathway. Resveratrol treated tumors were more organized with fewer cellular components and more collagenous structures
2	Tsung-Teng Huang et al[29] (2010)	In vitro	Human NPC cell lines (TW076, CG-1, TW04)	Increased the activity of caspases-8 and 9, induced loss of mitochondrial membrane potential and release of cytochrome c to cytosol in TW04 cells and modulated the level of Bcl-2 family proteins leading to induced apoptosis of NPC cell lines

PI3K, Phosphatidylinositol 3' kinase

DISCUSSION

Resveratrol as an anticancer agent has shown a great promise and in this study, we tried to highlight the property by doing the systematic analysis of various published research. Our analysis of the data published in the last few years has brought about anticancer role of resveratrol in colorectal carcinoma (Table 1), breast carcinoma (Table 2), Haematological malignancies (Table 3), Skin tumours (Table 4), Prostate cancer (Table 5), Nasopharyngeal carcinoma (Table 6). In studies conducted in vivo in human patients of colorectal carcinoma[7,8], resveratrol has shown the anticancer effect and cancer preventive effects. The possible mechanisms described were a decrease in tumour cell proliferation and suppression of Wnt pathway target gene (myc, jun, TCF-7, Axin II, Cyclin D1) expression in the normal colonic mucosa. Animal studies in vivo[9] on Dextran Sulphate sodium mouse model of colitis and colon cancer, resveratrol exhibited chemopreventive effect by decreasing the markers of inflammation and also the inhibition of infiltration of neutrophils in mesenteric lymph nodes. Also there was modulation of CD3+T cells that expressed TNF-α and IFN-γ. In vitro studies on human colon cancer cell lines confirmed the chemopreventive properties of resveratrol with the plausible mechanisms being increasing the cellular oxidative stress by increase in the levels of ROS (lipid peroxides) which might be an adjuvant effect to the growth inhibition by the anticancer drug 5-Flurouracil[10]. Decrease in the glycolytic enzymes, increase in the citrate synthase activity, decrease VEGF and down regulation of leptin and c-myc expression [11], suppression of IGF-1R/Akt/Wnt signalling and activation of p53 has shown proliferation suppression even in the presence of IGF-1[12]. Increased expression of apoptotic factor bax and decreased expression of antiapoptotic factor bcl-2 has shown the inhibition of cell growth by resveratrol at S phase of cell cycle[13].In breast carcinoma, human in vivo study[14], resveratrol showed inhibition of cancer proliferation by decreasing methylation of tumour suppressor gene RASSF-1α and cancer promoting prostaglandin PGE_2. In an in vitro study on breast cancer cell lines MCF-7, resveratrol antagonized the recruitment of AhR to the BRCA-1 promoter and the reduction of BRCA-1 expression in the mammary epithelial cells[15]. Resveratrol inhibited genes of mismatch repair, DNA replication, homologous recombination and cell cycle[16]. This could enhance the treatment efficacy of anticancer drugs and would also help in overcoming the chemoresistance. Resveratrol has shown its benefit in haematological cancers too. In a human study (ex vivo)[17], the peripheral blood and bone marrow mononuclear cells of untreated CLL patients and in an in vitro study[18], 232B4 human CLL cells were exposed to resveratrol and there was induction of apoptosis in the CLL cells and arrest of cell cycle in the G_0-G_1 phase due to the inhibition of ribonucleotide reductase. There was also upregulation of p53 and p21 tumour suppressor genes and induction of NO, decreased Bcl-2/Bax ratio resulting in

apoptosis. In vitro studies, on human HL60 APL cells[19] and human K562 CML cells[20] showed the apoptotic properties of resveratrol through accumulation of ceramides via up regulation of Longevity assurance gene (LASS) and suppression of Glucosyl ceramide synthase (GCS) and Sphingosine kinase -1 (SK-1) genes. Positive effects of resveratrol on skin cancer demonstrated by in vivo animal studies[21,22] in mice model, where resveratrol prevented UV and chemically induced skin cancers through decreased expression of phosphorylated MAPK family proteins, decreased expression of TGF-β_2 in UV induced squamous cell carcinoma by reducing Akt/cAMP response binding protein (CREB) mediated TGF-β_2 expression, thereby limiting the tumour progression. Down regulation of Akt by resveratrol is also studied in an in vitro study where resveratrol reduced the invasiveness of melanoma cells.[23] In an in vivo animal study and in vitro study, resveratrol decreased the viability of squamous cancer cell lines FaDu, Cal27 by anti-proliferative, DNA damaging and apoptotic effects.[24] Resveratrol showed increased apoptosis of human skin SCCA431 xenografts of squamous cell carcinoma cells through upregulation of p53.[25] Anticancer role of resveratrol in prostate cancer is through Akt inhibition and Akt mediated microRNA 21 inhibition.[26] Resveratrol showed both inhibition of cancer cell viability and the invasiveness in both androgen dependent and independent prostate cancer cells. In an in vitro study[27], resveratrol not only inhibited androgen receptor activity but also inhibited EGFR and HER2 phosphorylation and subsequent Akt phosphorylation in both androgen dependent and independent prostate cancer cells.Resveratrol also exhibited its anticancer effect in Nasopharyngeal carcinomas. In *in vitro* studies[28,29], on NPC cell lines CNE-2Z, TW04, TW076, resveratrol induced apoptosis of NPC cell lines by blocking PI3K/Akt signalling pathway, increasing the activity of caspases-8 and 9, and by release of cytochrome c in cytosol.

CONCLUSION

Cardiovascular beneficial effects of resveratrol are known for a long time, but since last few years focus has been shifted on its anticancer and chemopreventive properties too. Various mechanisms of resveratrol's anticancer activity have been described, but most of these studies are done *in vitro* in human and animal cell lines. Very few studies are available which have been conducted *in vivo* involving large cohorts of actual patients. In our study, we tried to compile and analysed the already published studies on the role of resveratrol in various cancers. With so many novel mechanisms of action involving multiple pathways of cancer suppression, chemoprevention and chemosensitization, resveratrol could become an important adjuvant in the fight against cancer, and we recommend human clinical trials involving large number of patients to really establish Resveratrol as an anticancer agent.

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