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Resveratrol-based combinatorial strategies for cancer management

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Abstract

In recent years, *combination chemoprevention* is being increasingly appreciated and investigated as a viable and effective strategy for cancer management. A plethora of evidence suggests that a combination of agents may afford synergistic (or additive) advantage for cancer management by multiple means, such as by (1) enhancing the bio-availability of chemopreventive agents, (2) modifying different molecular targets, and (3) lowering the effective dose of agents/drug to be used for cancer management. Resveratrol has been shown to afford chemopreventive as well as therapeutic effects against certain cancers. Recent studies are suggesting that resveratrol may be very useful when given in combination with other agent. The two major advantages of using resveratrol in combination with other agents are: (1) synergistically or additively enhancing the efficacy against cancer, and (2) limiting the toxicity and side effects of existing therapies. However, concerted and multidisciplinary efforts are needed to identify the most optimal combinatorial strategies.

Keywords

resveratrol; cancer; chemoprevention; combination chemoprevention

Introduction

Amassed research has suggested that a number of naturally occurring agents, including those present in human diet, may be useful against a variety of diseases including cancer. However, based on recent literature, it is becoming increasingly clear that a single-agent approach is probably less likely to be very effective in the management of diseases, including cancer. In fact, a combinatorial approach relying on a cocktail of drugs, rather than a single drug, has been in practice for disease management for a long time. As pointed out by Dr. Michael Sporn and also suggested by recent research, *combination chemoprevention* may be a more practical approach for cancer management.[1] In classical terms, chemoprevention is defined as a strategy to reduce the risk, or delay the development or recurrence, of cancer via drugs, vitamins, or other agents. However, recent studies have suggested the usefulness of a number of chemopreventive agents in therapeutic settings. Therefore, the definition of chemoprevention seems to have expanded to include the delay or even reversal of the process of carcinogenesis. It appears that combinatorial chemopreventive approaches could be effective in prevention as well as treatment of cancer. The effective combination chemopreventive approaches can make use of (1) a combination

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Conflict of Interest
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of multiple agents based on molecular targets, (2) a combination of existing drugs with chemopreventive agents, in adjuvant settings, and/or (3) a combination of agents, drugs and life style modifications.

Resveratrol, an antioxidant present in red grapes, red wine and a variety of other dietary sources, has been shown to possess many beneficial biological properties, including cancer chemopreventive effects. A plethora of studies, especially in the last fifteen years, has shown the cancer preventive and therapeutic potential of resveratrol in a variety of *in vitro* and *in vivo* models. In the recent past, resveratrol has arguably become the agent that holds the most fascination among researchers, the news media, and the general public. Some recent studies have also evaluated the combinatorial effects of resveratrol with other naturally occurring and chemotherapeutic agents, suggesting that resveratrol can improve the efficacy of other agents.[2–8] Indeed, the strategy of using resveratrol in combination with other agents, particularly with chemotherapeutic modalities, holds a clinical promise in cancer management. However, evidence-based scientific evaluations in appropriate models are needed to show the efficacy of resveratrol in combination with other agents. This review provides a discussion and perspective on the potential of resveratrol-based combinatorial strategies for cancer management.

Resveratrol amid many of nature's gifts

Resveratrol, chemically known as 3,5,4′-trihydroxy-trans-stilbene, is a strong antioxidant that has been identified in over 70 plant species, including grape skin, raspberries, blueberries, mulberries, Scots pine, Eastern white pine, and knotweed. Resveratrol is a phytoalexin, synthesized *de novo* by plants during environmental stress and pathogenic invasion, thereby acting as a natural inhibitor of cell proliferation.[9] The use of resveratrol for health benefits can be traced back to several ancient medicine systems. For example, resveratrol has been a component of “Darakchasava,” an ancient Ayurvedic herbal formulation.[10] However, resveratrol was first isolated by Michio Takaoka from the roots of *Veratrum grandiflorum* (white hellebore) in 1940 (reviewed in Timmers *et al.*).[11] In 1963, he extracted resveratrol from the roots of the plant *Polygonum cuspidatum* (Japanese knotweed). At present, most of the commercially available resveratrol is isolated from *Polygonum cuspidatum* using high-speed counter-current chromatography.[12] The popularity of resveratrol started rising in 1992 when its occurrence was noticed in red wine and it was linked to “French Paradox,” the apparently paradoxical epidemiological observation that the French population possesses a lower risk of coronary heart disease, despite consuming a diet rich in saturated fats.[11] Following this, scientific research on resveratrol surged at an astronomical pace. Although resveratrol exists in both *cis*- and *trans*-stereoisomeric forms, the commercially available resveratrol is mainly the *trans*-form and that has been most extensively studied. Because of its strong antioxidant properties, resveratrol is being extensively studied in a variety of oxidative stress–associated diseases. A number of studies have shown the benefits of resveratrol against a variety of diseases and conditions including heart disease, neurological disorders, metabolic disorders, and degenerative conditions. Resveratrol has also been shown to improve immune function and mimic the life-lengthening effects of calorie restriction without dieting. The cancer chemopreventive properties of resveratrol were first appreciated in 1997, when Jang and colleagues found that resveratrol possesses chemopreventive activity against all the three major stages of carcinogenesis (i.e., initiation, promotion and progression).[13] This was followed by an extensive effort of researchers to determine the cancer chemopreventive and therapeutic effects of resveratrol in a wide range of models.

Resveratrol for cancer management

Popularity of resveratrol in cancer chemoprevention research could be appreciated from its continuously growing records in PubMed as well as the clinical trial databases. Based on published studies, there is sufficient evidence that resveratrol possesses promise in chemoprevention of several cancer types. Below, we have provided a very brief description on selected published studies suggesting chemopreventive/antiproliferative effects of resveratrol against some cancer types.

Several studies have suggested that resveratrol could be useful against prostate cancer, which is a major neoplasm of males and represents an ideal candidate disease for chemoprevention due to its long latency and identifiable pre-neoplastic lesions. Resveratrol has been demonstrated to impart chemopreventive effects in relevant animal models of prostate cancer. Harper and colleagues have shown that resveratrol reduced the incidences of poorly differentiated prostatic adenocarcinoma by several folds in the transgenic adenocarcinoma of mouse prostate (TRAMP) model.[14] Seeni and colleagues have demonstrated that resveratrol suppresses prostate cancer growth in the transgenic rat for adenocarcinoma of prostate (TRAP) model.[15]

The first evidence regarding the possible skin cancer chemopreventive efficacy of resveratrol comes from the study by Jang *et al.* that demonstrated chemopreventive effects of resveratrol in the classic chemical carcinogenesis model.[13] Since ultraviolet (UV) light is believed to be the major cause of skin cancer, in a series of studies from our laboratory, we demonstrated the protective potential of resveratrol against UV-mediated damage in skin (reviewed in Ndiaye *et al.*).[16] In an important study, employing a UVB initiation–promotion protocol we demonstrated that the topical application of resveratrol resulted in a significant inhibition in skin tumor incidence as well as delay in the onset of tumorigenesis in an SKH-1 hairless mouse model.[17] Following this study, several reports demonstrated the protective efficacy of resveratrol against skin cancer (reviewed in Ndiaye *et al.*).[16] In addition, resveratrol has also been shown to be effective in syngeneic melanoma mouse models.[18] Similarly, a number of studies have demonstrated the potential efficacy of resveratrol against breast cancer,[19] gastric cancer,[20] colorectal cancers,[21–23] and other cancer types such as cancers of lung, liver, pancreas and bladder.[24–27] Thus, resveratrol has been extensively studied for cancer chemoprevention and may have the potential to become an ideal agent for cancer management. Further, resveratrol does not seem to have toxicity and has been shown to be reasonably well-tolerated at doses of up to 5 g/day in healthy subjects without any side effects.[28] However, the effective dose of resveratrol depends on disease and subject context, and still needs to be investigated.

Combination chemoprevention from ancient to modern time

The concept of combination chemoprevention is not a new idea. Most of the world's ancient medicine systems seem to have relied on multiple agents to try to target many symptoms at the same time. *Ayurveda* (meaning “the science of long life” in Sanskrit), or ayurvedic medicine, an approximately 5000-year-old system of traditional medicine native to the Indian subcontinent, often uses a combination of herbs and agents for disease management. Ayurveda is still in practice in the Indian subcontinent for management for diseases including cancer.[29] There is an extensive list of herbs which are used, often in combinations, in the Ayurvedic management of cancer. Some of these, which have been tested and supported by modern research to have antiproliferative efficacy, include *Curcuma longa* (turmeric), *Aloe vera* (aloe), *Allium sativum* (garlic), *Abrus precatorium* (coral bead vine), *Boswellia serrata* (Indian olibanum), *Plumbago zeylanica* (leadwort) and *Vinca rosea* (periwinkle).[29] Interestingly, the herbal Ayurvedic tonic formulation Darakchasava, which is

used for good health, has been shown to contain resveratrol and pterostilbene.[10] Similarly, the traditional Chinese medicine system, which also has a more than 5000-year-old history, is also based on a cocktail approach. Traditional Chinese herbal cocktails are often used as complementary medicine approaches to manage diseases, including in cancer to diminish the side effects and/or tumor resistance to chemotherapy/radiotherapy.[30] Interestingly, a cocktail of Chinese herbs (containing spreading hedyotis herb, barbed skullcap herb, ma-yuen Job's tears seed, *Ganoderma lucidum*, and Chinese hawthorn fruit), in conjunction with chemotherapy and radiation therapy, was shown to have favorable clinical outcome in pancreatic cancer patients with liver metastases.[31] Nature also seems to support a combinatorial approach, since our food is believed to be a conglomeration of numerous beneficial ingredients. Based on emerging scientific evidence, the “whole foods” concept is being viewed as a better approach than a single dietary factor. It is believed that individual dietary factors in food may work additively or synergistically, to yield a better response in preventing diseases.

In modern times, the concept of multi-agent therapeutics for cancer treatment has been in practice since the 1960s, with evidence of enhanced survival in childhood leukemias and Hodgkin's disease following combination chemotherapy (compared to a single agent).[32] Currently, most cancer chemotherapeutic drugs are used in combination in order to increase efficacy and/or decrease toxicity. The rationale for recommending a multi-drug regimen is to attack more than one critical function in the cancer cells, leading to improved clinical outcomes. Thus, from ancient times to the modern era, combinatorial therapeutic strategies for disease management have been proven to be more efficacious than monotherapies. Based on recent studies and strong rationale, combination chemoprevention is being appreciated and investigated as a viable and effective strategy for cancer management.

Resveratrol-based combinations for cancer management

Based on encouraging recent research in a wide range of scientific disciplines, including cancer, heart diseases, metabolic conditions, and aging, resveratrol is probably the most extensively studied flavonoid at present. Recently, researchers began to focus on using resveratrol in conjunction with other agents and drugs for improved response against cancer. A few examples of recent research efforts on resveratrol-based combinatorial strategies are discussed below. In this review, we have mainly focused on *in vivo* studies conducted in animal models. Table 1 provides a summary of *in vivo* studies where resveratrol-based combinations have been evaluated.

Resveratrol and piperine

A group of researchers believe that the biggest hurdle in the development of resveratrol as a drug or preventive agent is its poor bioavailability following oral ingestion, due to its rapid metabolism, mainly to its glucuronide and sulfate metabolites. We have recently reviewed this area of research and the different possibilities in this direction.[33] We believe that more research is needed to determine the possibility of chemopreventive efficacy of resveratrol metabolites as well as the possibility of obtaining and maintaining steady and effective *in vivo* resveratrol concentrations following chronic ingestion. However, researchers have begun to focus on different means of enhancing the bioavailability of resveratrol, as well as developing novel resveratrol analogues with superior efficacy and bioavailability. A recent study from our laboratory has shown that piperine, an alkaloid present in black pepper, can significantly enhance resveratrol levels in the blood of mice.[34] In this study, we found that addition of piperine significantly enhances the degree of exposure (i.e., AUC) to resveratrol as well as its maximum serum concentration (C_{max}) in C57BL mice.[34] Piperine has previously been shown to enhance the bioavailability of other polyphenols such as (-)-epigallocatechin-3-gallate (EGCG).[35] In another interesting recent *in vitro* study, a

resveratrol and piperine combination was found to act as a sensitizer for ionizing radiation–induced apoptotic cell death.[5] Although these studies are encouraging, the effect of piperine on resveratrol bioavailability remains unknown in the human population. Further, the therapeutic efficacy of this combination in disease models needs to be assessed.

Resveratrol and quercetin

Both resveratrol and quercetin are polyphenols present in red grapes, red wine and several other plants. However, the levels of quercetin in red wine are typically ~10-fold higher than resveratrol.[36] In a recent study, Khandelwal *et al.* have shown that resveratrol and quercetin synergistically reduce the extent of restenosis (a critical complication of angioplasty and stenting), possibly by inhibiting vascular smooth muscle cell proliferation and inflammation.[36] Further, in a study by Zhou *et al.*, transcriptomic and metabolomic profiling revealed the synergistic effects of quercetin and resveratrol supplementation in high-fat diet–fed mice.[37] It seems that additive/synergistic interactions between these two polyphenols may be one explanation for the “French Paradox”, especially because both of these agents are present in red wine. Thus, the combination of resveratrol and quercetin seems to have potential towards cancer management. In addition, quercetin has also been shown to inhibit sulfation of resveratrol.[38] Therefore, it is conceivable that quercetin can enhance the bioavailability, and thus therapeutic efficacy, of resveratrol by inhibiting its sulfation. However, studies are needed to explore these possibilities.

Resveratrol and melatonin

Resveratrol has also been studied in combination with the pineal hormone and known antioxidant melatonin. Kiskova and colleagues have recently demonstrated that a combination of resveratrol with melatonin exerts superior chemopreventive effects in N-methyl-N-nitrosourea (NMU)–induced rat mammary carcinogenesis.[6] The data from this study showed that neither of the two agents alone had any appreciable effect on NMU-induced mammary carcinogenesis, the combination resulted in a significant decrease in tumor incidence. Further, another study found that melatonin synergistically enhanced resveratrol-induced heme oxygenase-1, possibly through inhibition of a ubiquitin-dependent proteasome pathway.[39] The authors suggested that this combination may provide an effective means to treat neurodegenerative disorders.[39] This combination seems to have potential in cancer chemoprevention. It is possible that these two agents may target two non-overlapping pathways. While melatonin can function through its own receptors, resveratrol may inhibit proliferative signaling by modulating other pathways. Thus, there is a possibility that this combination may lead to a synergistic response to attenuate proliferative signaling and improve cancer chemopreventive response.

Resveratrol and tea polyphenols

In a recent study, George and colleagues determined the effect of the combination of resveratrol with black tea polyphenol in a two-stage mouse skin carcinogenesis model. It was found that the combination imparts a synergistic tumor-suppressive response, compared to either of the agents alone.[7] The authors suggested that the observed synergistic response is possibly due to a synergistic action of the two agents on same molecular targets. This is an interesting study because a synergistic action of multiple agents on a common pathway(s) can lead to dose-reduction of chemopreventive agents, thereby limiting the chances of side effects.

Resveratrol and curcumin

In a recent study, Malhotra *et al.* assessed the efficacy of combined supplementation of curcumin and resveratrol in benzo[a]pyrene (BP)-induced lung carcinogenesis in mice.[25]

The study demonstrated that curcumin and resveratrol in combination provide a better chemopreventive response by maintaining adequate zinc levels and by modulating Cox-2 and p21.[25] Here, it is important to mention another study by Zhang *et al.*, which demonstrated that a combination of resveratrol and zinc in normal human prostate epithelial cells increased total cellular zinc and intracellular free labile zinc in the cells.[40] Since zinc is an extremely important trace element in normal prostate development as well as in prostate cancer, this finding provides a rationale to conduct further studies to evaluate the combination of zinc and resveratrol in prevention as well as treatment of prostate cancer.

Combination with other natural agents

A few other combinations containing resveratrol have also been investigated for their cancer chemopreventive effects in *in vivo* models. Slusarz and colleagues determined the preventive and therapeutic abilities of a number of agents along with resveratrol (quercetin, genistein, apigenin, baicalein, curcumin, and (EGCG)), *in vitro* as well as *in vivo* in (TRAMP).[41] The authors found that four of the seven compounds (genistein, curcumin, EGCG, and resveratrol), inhibited Hedgehog signaling as shown by real-time reverse transcription–PCR analysis of Gli1 mRNA concentration or by Gli reporter activity.[41] The authors also found that all the seven compounds, when fed in combination as pure compounds or as crude plant extracts, inhibited well-differentiated carcinoma of the prostate by 58% and 81%, respectively. In another study, resveratrol in combination with genistein, provided in the diet, was found to significantly reduce the most severe grade of prostate cancer in the Simian Virus-40 T-antigen (SV-40 Tag)–targeted probasin promoter rat model, a transgenic model of spontaneously developing prostate cancer.[4] In another study, Jiang and colleagues have shown the anti-cancer efficacy of the dietary supplement ProstaCaid™, which contains a number of chemopreventive agents including resveratrol, against invasive prostate cancer in a nude mouse model.[42]

Resveratrol in combination with anticancer drugs

Plenty of *in vitro* and limited *in vivo* studies have suggested that resveratrol may enhance the antitumor effects of chemotherapeutic drugs in several cancers.[43, 44] Thus, in addition to chemopreventive and cytostatic properties, resveratrol is being investigated for its potential as an adjuvant in conjunction with chemotherapeutic modalities to enhance their efficacy and/or limit their toxicities. Lin and colleagues have shown that resveratrol potentiated the therapeutic efficacy of temozolomide, an alkylating agent used in cancer therapeutics, in a mouse xenograft model of malignant glioma, through inhibiting ROS/ERK mediated autophagy and enhancing apoptosis.[45] Resveratrol has also been shown to overcome chemoresistance in a mouse model of B16/DOX melanoma by inducing cell cycle disruption and apoptosis, leading to reduced growth of melanoma and prolonged survival of mice.[46] In a recent study, a combination of the dietary grape polyphenols resveratrol, quercetin, and catechin was shown to potentiate the effects of gefitinib in inhibiting mammary tumor growth and metastasis in nude mice.[8] These studies support the potential use of resveratrol as an adjuvant in combination with chemotherapeutic drugs for cancer management. However, one study by Fukui *et al.* suggested that resveratrol may diminish the anti-proliferative effect of paclitaxel in breast cancer.[47] Therefore, more preclinical studies in appropriate model are warranted to ascertain the usefulness of resveratrol as an adjuvant.

Resveratrol in combination with other factors within its natural matrix

As discussed above, emerging evidence are suggesting that the whole foods concept could be a better approach than single agents due to the possibility of synergistic improvement of responses from interactions between different ingredients within a food source. For example, grapes contain several hundreds of ingredients with health-promoting properties. These individual agents may enhance the effectiveness and bioavailability of each other. Careful

studies are needed to understand and to define whether an agent(s) should be considered in isolation, in combination, or in its natural complex form. A few examples of resveratrol–based naturally occurring combinations are provided below.

Crude extract of *Polygonum cuspidatum*, in addition to resveratrol, contains piceid (a glucoside precursor of resveratrol), polydatin (a stilbene) and emodin (an anthraquinone), among several other ingredients. All of these agents are considered as potential bioactive agents with health–promoting effects. A study by Ghamin *et al.* assessed the effect of a *Polygonum cuspidatum* extract (PCE) containing resveratrol on oxidative and inflammatory stress in healthy volunteers. Based on the data, the authors suggested that the PCE containing resveratrol had a comprehensive suppressive effect on oxidative and inflammatory stress.[48] In another phase I pilot study in colorectal cancer patients, Nguyen and colleagues found that resveratrol-containing freeze-dried grape powder inhibits the Wnt pathway, which is a key signaling pathway in colon cancer initiation; however, the effect was confined to the normal colonic mucosa.[49] Ortuno and colleagues conducted a pharmacokinetic study of resveratrol, in different matrices, in eleven healthy volunteers. The authors found that resveratrol was better absorbed from natural grape products than from supplements.[50] All of this evidence suggested that naturally available combinations of resveratrol and matrix of the source may be extremely important to the overall bioavailability and efficacy of resveratrol. This seems to be very important in cancer prevention settings, where chronic administration of resveratrol-containing moieties can possibly lead to an effective concentration of resveratrol *in vivo* to provide a chemopreventive response.

Conclusions

Based on emerging evidence, it is becoming increasingly clear that combination chemoprevention, relying on a combination of agents with limited (non-overlapping) toxicity, which may diminish the toxicity of each other while enhancing therapeutic efficacy, could be a better strategy for cancer management. Resveratrol is being extensively studied for chemoprevention in a variety of cancers. It appears that resveratrol possesses a number of characteristics of an ideal chemopreventive agent, such as (1) a lack of toxicity at desired concentrations, (2) available knowledge of mechanism(s) of action, (3) human acceptability because of being a dietary ingredient, and (4) cost affordability. Recent research is focusing on resveratrol-based combinatorial strategies for the management of cancer. As discussed before and depicted in Figure 1, resveratrol based combinations can lead to improved chemopreventive and therapeutic response in a number of ways. On one hand, resveratrol may be used in combination with other naturally-occurring chemopreventive agents in a cancer prevention setting. On the other hand, resveratrol may be used in conjunction with existing therapeutic modalities to enhance their response and limit their toxicity. Indeed, further preclinical studies are required to define the most useful combinations. In addition, clinical studies are also needed to ascertain the efficacy of resveratrol in adjuvant settings.

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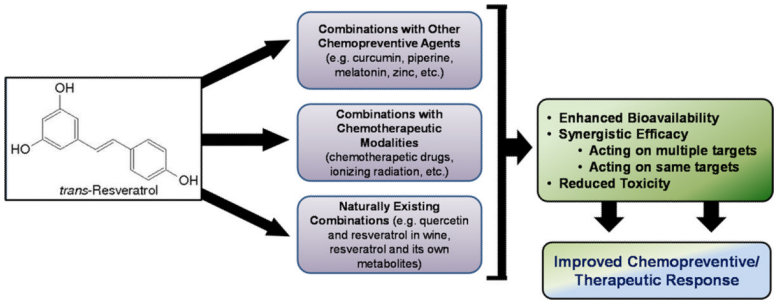

Figure 1.
Resveratrol-based combinatorial strategies for cancer management

Table 1

Studies evaluating combinations of resveratrol with other agents.

Agents used in combination with resveratrol	Model System	Outcome	References
Piperine	C57BL healthy mice	Piperine enhanced the serum bioavailability of resveratrol.	34
Quercetin	Mice with a carotid injury	Combination synergistically reduced the extent of restenosis.	36
Quercetin	High-fat diet–fed mice	Combination resulted in a restoration of high fat–induced alterations in pathways of glucose/lipid metabolism, liver function, cardiovascular system, and inflammation/immunity.	37
Melatonin	NMU-induced rat mammary carcinogenesis	Combination resulted in a significant decrease in tumorigenesis.	6
Black tea polyphenols	Two stage skin carcinogenesis mouse model	Combination resulted in a synergistic tumor suppressive response.	7
Curcumin	BP-induced lung cancer in mice	Combination showed better chemopreventive response by maintaining adequate zinc, and modulating Cox-2 and p21 level.	25
Quercetin + Genistein + Apigenin + EGCG + Baicalein + Curcumin	TRAMP mouse model of prostate cancer	All seven compounds inhibited well-differentiated carcinoma of the prostate by 58% when fed in combination as pure compounds; and 81% when fed as crude plant extracts.	41
Geneistin	SV-40 rat model of prostate cancer	Combination reduced the most severe grade of prostate cancer in SV-40 Tag–targeted probasin promoter rat model	4
ProstaCaid	Nude mouse model of prostate cancer	ProstaCaid™, which contains a number of chemopreventive agents including resveratrol, inhibited invasive prostate cancer in a nude mouse model	42
Temozolomide	Nude mouse model of glioma	Resveratrol was found to enhance the therapeutic efficacy by inhibiting ROS/ERK-mediated autophagy and enhancing apoptosis.	45
Doxorubicin (DOX)	B16/DOX mouse model of melanoma	Resveratrol was found to overcome chemoresistance by inducing cell cycle disruption and apoptosis.	46
Quercitin + Catechin + Gefitinib	Nude mouse model of mammary cancer	Resveratrol, quercetin and catechin combination potentiated the effects of gefitinib in inhibiting mammary tumor growth.	8