World Journal of Gastroenterology

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DOI: 10.3748/wjg.v21.i37.10636

World J Gastroenterol 2015 October 7; 21(37): 10636-10643
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

MINIREVIEWS

Resveratrol: A potential challenger against gastric cancer

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Author contributions: All authors contributed to the manuscript preparation and revision.

Conflict-of-interest statement: The authors declare no conflict of interest.

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Received: May 18, 2015
Peer-review started: May 20, 2015
First decision: June 23, 2015
Revised: July 9, 2015
Accepted: August 31, 2015
Article in press: August 31, 2015
Published online: October 7, 2015

Abstract

Gastric cancer (GC) is the fourth most common cancer and the second leading cause of cancer-related mortality in the world. Late diagnosis and classical therapeutic approaches such as surgery, chemotherapy and radiotherapy make this disease a still threatening tumor. Genetic asset, environmental stress, dietary habit and infections caused by *Helicobacter pylori* (*H. pylori*) are the major causes concurring to GC initiation. A common mechanism is induction of radicals resulting in gastric mucosal injury. A regular food intake of antioxidant and radical scavenging agents has been proposed to exert protection against tumorigenesis. Resveratrol belongs to the polyphenol flavonoids class of antioxidants produced by a restricted number of plants. Resveratrol exerts bactericidal activity against *H. pylori* and is a powerful antioxidant, thus acting as a tumor preventive agent. Resveratrol intracellular signaling results in growth arrest and apoptosis, so that it can be directed against tumor progression. Resveratrol therapeutic potential against GC initiation and progression are reviewed here.

Key words: Resveratrol; Polyphenols; Gastric cancer; Diet; Cell cycle; Apoptosis

Core tip: Gastric cancer (GC) is the fourth most common cancer and the second leading cause of cancer-related mortality in the world. Despite the improvement of conventional therapies for advanced GC, the length or quality of life of patients with advanced GC is still poor. Resveratrol exerts bactericidal activity against *Helicobacter pylori*, acting as a GC preventive agent. Resveratrol therapeutic potential against GC initiation and progression is thus required to be surveyed and this is done within this minireview.

Zulueta A, Caretti A, Signorelli P, Ghidoni R. Resveratrol: A potential challenger against gastric cancer. *World J Gastroenterol* 2015; 21(37): 10636-10643 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i37/10636.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i37.10636

INTRODUCTION

Gastric cancer (GC) is the fourth most common

cancer and the second leading cause of cancer-related mortality in the world[1], due to the difficulty in making an early diagnosis for GC, thus most of the patients are diagnosed at advanced stages. Despite the improvement in conventional therapies for advanced GC, including surgery, chemotherapy and radiotherapy, the length or quality of life of patients with advanced GC is still poor[2,3]. There is therefore an urgent need to explore new preventive drugs or therapeutic targets.

Although the host genetic asset, environmental stress, dietary habits and other factors have been implicated in the gastric oncogenic process, there is strong evidence that the predominant etiological factors contributing to the development of GC are infections caused by *Helicobacter pylori* (*H. pylori*) and/or exposure to chemical carcinogens such as those in cigarettes and cured meats[1,4-6]. The identification and eradication of *H. pylori* infection in the world population would be an economically prohibitive undertaking because more than 50% of the population over the age of 50 is infected with the bacterium, and eradication would not benefit those with pre-malignant gastric mucosal alterations. The infiltration of neutrophils and macrophages caused by *H. pylori* infection leads to the production of free radicals, including nitric superoxide and oxide. ROS-mediated stress responses result in gastric mucosal injury, ulcers, and ultimately GC[7]. Therefore, agents that have a powerful antioxidant potential *via* ROS scavenging or enhancing antioxidant capacity may help to protect against GC initiation and progression.

Among antioxidants, an important role is played by natural compounds with radical scavenging activity, that can be ingested on a regular basis by food intake and exert protection against tumorigenesis. Polyphenols comprise a large class of antioxidants and include flavonoids, anthocyanins, phenolic acids, lignans and stilbenes. These compounds are all derived from phenylalanine and contain an aromatic ring with a reactive hydroxyl group. Within the subclass of stilbenes, resveratrol is the common term for 3,5,4'-hydroxystilbene. Resveratrol is produced by a restricted number of plants (about 31 genera). It is not normally present in large amounts and is produced in response to stress; resveratrol belongs to a class of defense molecules called phytoalexins that protect against infection and damage from exposure to ultraviolet (UV) irradiation[8-10]. Resveratrol and the analogs piceatannol and pterostilbene have been found in several edible natural products such as grapes (*Vitis* spp.), peanuts (*Arachis* spp.)[11], berries (blueberries, cranberries and lingonberries, all *Vaccinium* spp.) [12] and rhubarb (*Rheum* spp.)[13].

Resveratrol was first reported to exert anti-tumor activities in 1997[14]. Since then, the antioxidant, anti-inflammatory, anti-proliferative, and anti-angiogenic effects of resveratrol have been widely studied[15]. Subsequent reports have shown that resveratrol suppresses proliferation of several types of cancers, such as colon, breast, pancreas, prostate, ovarian and endometrial cancers, as well as lymphoma, and affects diverse molecular targets[16-23]. In this review, we will summarize the principal findings that support the antitumoral properties of resveratrol in GC either as a preventive or as a therapeutic agent.

PREVENTIVE ROLE OF RESVERATROL IN GC AGAINST *H. PYLORI*

Besides its antioxidant activity, resveratrol was found to have antimicrobial effects[24] by inhibiting the growth of multiple *H. pylori* strains[25-27]. The infection by *H. pylori* induces an inflammatory response with the release of various cytokines and reactive oxygen species and changes in cell proliferation[28]. The neutrophil attractant IL-8 is one of the most crucial chemokines in the host inflammatory response to *H. pylori*[29-33]. The upregulation of IL-8 following *H. pylori* infection may lead to free-radical generation, and the release of proteolytic enzymes from activated neutrophils ultimately affects mucosal integrity[28]. Pre-treatment of *H. pylori*-infected MKN-45 cells with resveratrol at 75 and 100 μmol/L for 4 h significantly suppressed IL-8 secretion. Moreover, ROS production was significantly suppressed by resveratrol pre-treatment at 10-100 μmol/L for the same time[34].

Another peculiarity of *H. pylori* infection is the increased severity in patients infected by strains expressing the CagA (cytotoxin associated gene A) which are endowed with an increased inflammatory potential[35]. It has been documented that the interaction between CagA positive *H. pylori* strains and host cells is associated with morphological changes that lead to dysregulation of host cell functions, thereby contributing to pathogenesis. After CagA protein injection by *H. pylori* into the cells, CagA interacts with various intracellular signaling molecules including enzymes like Src kinases, eventually leading to increased cell motility and the hummingbird phenomenon[36]. Resveratrol pre-treatment (100 μmol/L) for 2 h blocked the morphological changes induced by infection with a CagA positive *H. pylori* strain in the MKN-45 cells[34]. Resveratrol may be a particularly important preventive tool in GC since *H. pylori* strains isolated from gastric carcinoma biopsies show an increased susceptibility to resveratrol compared with strains isolated from patients with chronic gastritis alone[37]. The hypothesis is that one target of the antibacterial action of resveratrol may be one or more F-type ATPases, which normally protect the bacteria from low pH levels by maintaining a proton gradient across membranes. In strains isolated from patients with gastric carcinoma, such an enzyme may be underexpressed, as an adaptive response to an environment that has lost its natural acidity. Thus, the bacterial defenses are reduced and then susceptibility to resveratrol is increased, so that it saturates its

targets more quickly and efficiently.

RESVERATROL AS A THERAPEUTIC AGENT IN THE INHIBITION OF CANCER CELL PROLIFERATION

Resveratrol arrests proliferation and induces apoptosis in vitro

In addition to its bactericidal properties, there is multiple evidence that resveratrol is able to inhibit cell proliferation of human adenocarcinoma cell lines, but the mechanisms underlying its action remain unknown. Since resveratrol has been shown to mediate apoptosis through a variety of different pathways[38-40], resveratrol-induced apoptosis seems to be one of the inhibitory mechanisms in GC. Several authors have shown that the resveratrol-induced apoptotic program is consequent to its inhibition of cell proliferation. Atten *et al*[41,42] found that exposure of KATO-Ⅲ and RF-1 cells[41] and SNU-1 cells[42] to resveratrol (100 μmol/L for 24 h) interfered with cell cycle progression, inhibited DNA synthesis and suppressed cellular proliferation. Moreover, resveratrol suppressed nitrosamines-stimulated DNA synthesis in RF-1 cells, showing that, in addition to suppressing normal cellular proliferation, resveratrol was able to reverse carcinogen-stimulated proliferation. Resveratrol induced inhibition of protein kinase C (PKC) activity in KATO-Ⅲ cells, without any change in mitogen-activated protein kinases ERK1/ERK2 activity, suggesting that resveratrol utilizes a PKC-mediated mechanism to inhibit growth of gastric adenocarcinoma cells[41]. This finding is significant when considering that inhibitors of PKC have been studied as potential anticancer agents precisely because they are associated with tumor suppression, cell cycle arrest, decreased proliferation, and apoptosis[43]. Gastric adenocarcinoma SNU-1 cells treated with resveratrol showed a time- and concentration-dependent increase in tumor suppressors p21($^{cip1/WAF-1}$) and p53 preceded by the loss of membrane-associated PKC δ protein and by a concomitant increase in cytosolic PKC α[42]. Resveratrol also caused a time-dependent accumulation of Fas and Fas-L proteins in SNU-1 cells while it had no effect on Fas but did elevate Fas-L in p53 deficient KATO-Ⅲ cells[42]. Riles *et al*[44] found that individual gastric carcinoma cell lines respond to resveratrol (100 μmol/L) with engagement of individual apoptotic signals. They investigated the role of p53 in the intracellular apoptotic signals engaged by resveratrol. Resveratrol induced a time-dependent apoptotic response in the three cell lines analyzed irrespective of their p53 status. In p53 expressing SNU-1 cells resveratrol up-regulated p53 and down-regulated surviving, whereas in KATO-Ⅲ cells (not expressing p53) and in AGS cells, resveratrol stimulated caspase 3 and cytochrome C oxidase activities, enabling suppression of proliferation while stimulating the breakdown of nuclear proteins[44].

Treatment with resveratrol (50-200 μmol/L) for 48 h significantly induced apoptosis and DNA damage in human GC SGC-7901 cells[45]. These effects were due to the increased generation of ROS following resveratrol treatment, corroborated by the fact that incubation of cells with superoxide dismutase or catalase attenuated resveratrol-induced cellular apoptosis. Exposure to resveratrol (100 μmol/L) for 24 h induced cell death and cell cycle arrest in SNU-1 GC cells and the combination of resveratrol and dimethylsphingosine increased cytotoxicity, demonstrating that sphingolipid metabolites intensify resveratrol activity[46].

Resveratrol arrests proliferation without induction of apoptosis

Recent studies show a significant anti-proliferative effect of resveratrol in the absence of apoptosis induction, raising the hypothesis of alternative mechanisms, possibly depending on cell type or more likely on treatment dose, underlying the antitumoral activity of this polyphenol. Yang *et al*[47] found that resveratrol inhibited the proliferation of the GC cell lines AGS, BGC-823 and SGC-7901, inducing senescence instead of apoptosis. At concentrations of 25 and 50 μmol/L, resveratrol inhibited the cell viability and diminished the clonogenic potential of GC cells. Resveratrol treatment induced G1 phase arrest, and regulators of the cell cycle and senescence pathways, including cyclin D1, cyclin-dependent kinase (CDK4 and 6), p21 and p16, were dysregulated. In agreement with the proposed epigenetic activities of resveratrol *via* activation of the class Ⅲ nicotinamide adenine nucleotide (NAD^+)-dependent histone/protein deacetylase Sirt1[16,17], the compound inhibited both the proliferation of GC cells *in vitro* and the growth of tumor *in vivo* in a Sirt1 dependent manner[47]. Specifically, SIRT1 activation by resveratrol treatment in GC cells (AGS and MKN-45) not only diminished the levels of the acetylated forms of STAT3 and NF-κB, whose activity is associated with tumor progression[48,49], but also caused a loss of viability and an increase in senescence, which were rescued by SIRT1 inhibitor (nicotinamide) or SIRT1-depletion[47,50]. These results suggest that the inhibitory effects of resveratrol on GC may depend on Sirt1. However, some authors dispute this hypothesis, suggesting that resveratrol exerts chemoprotective effects independently of Sirt1[18].

Another proposed pathway involved in the mechanism of cell proliferation inhibition by resveratrol is the MEK1/2-ERK1/2- c-Jun signaling cascade. It has been documented that resveratrol treatment (500 nmol/L) abolished cell proliferation through specific inhibition of MEK1/2-mediated ERK1/2 phosphorylation, which consequently suppresses translocation of c-Jun into the nuclear compartment, impairing cell

Table 1 Summary of principal effects of resveratrol treatment on gastric cancer

Cell or animal model	Effect	First author	Year	Ref.
MKN-45 cells	Antioxidant and anti-inflammatory	Zaidi	2009	[34]
Helicobacter pylori strains	Bactericidal	Martini	2011	[37]
KATO-Ⅲ and RF-1 cells	Cell cycle arrest and pro-apoptotic	Atten	2001	[41]
SNU-1 cells	Cell cycle arrest and pro-apoptotic	Atten	2005	[42]
SNU-1, KATO-Ⅲ and RF-1 cells	Pro-apoptotic	Riles	2006	[44]
SGC-7901 cells	Pro-apoptotic	Wang	2012	[45]
SNU-1 and SNU-668 cells	Cell cycle arrest and anti-proliferative	Shin	2012	[46]
AGS, BGC-823 and SGC-7901 cells	Cell cycle arrest and senescence	Yang	2013	[47]
AGS and MKN-45 cells	Anti-proliferative and senescence	Lu	2014	[50]
AGC cells	Anti-proliferative	Aquilano	2009	[51]
HGC-27 cells	Cell cycle arrest	Signorelli	2009	[52]
Nude mice xenografts (BGC-823 cells)	Anti-proliferative	Yang	2013	[47]
Nude mice xenografts (primary gastric cancer cells)	Apoptosis of carcinoma cells	Zhou	2005	[57]

proliferation of human adenocarcinoma gastric cells (AGS)[51].

Resveratrol has been proposed to modulate sub-pools of sphingolipids, lipid molecules involved in structural as well as signaling functions, thus finely acting to block cell cycle with no direct apoptosis induction[46,52]. Resveratrol was found to downregulate the activity of dihydroceramide desaturase, the enzyme involved in ceramide formation along the *de novo* sphingolipid synthetic pathway, inducing dihydroceramide accumulation in GC cells[46,52]. Twenty-four hours' treatment with resveratrol (50 μmol/L) induced lack of cell death *via* apoptosis and enhanced autophagy in the HGC-27 cell line[52]. Dihydroceramide accumulated in a resveratrol concentration-dependent manner in other gastric cell lines like SNU-1, but not in SNU-668 cells[46] suggesting that the different sensitivity of cancer cells to resveratrol might be deeply related to sphingolipid, especially dihydroceramide, distribution patterns. In spite of the results reported, resveratrol was shown to induce ceramide increase and apoptosis in cancer cell lines other than gastric such as prostate[53], breast[54], and myeloid leukemia cells[55,56].

RESVERATROL ANTITUMORAL EFFECTS IN ANIMAL MODELS

The inhibitory effects of resveratrol on GC were also verified *in vivo* using nude mice xenograft models. Resveratrol (40 mg/kg per day) exerted inhibitory activities on GC development and significantly decreased the fractions of Ki67-positive cells in the tumor specimens from the nude mice[47].

Resveratrol significantly inhibited carcinoma growth when it was injected near the carcinoma in a tumor model established by transplanting human primary GC cells into subcutaneous tissue of nude mice[57]. An inhibitory effect was observed in all groups using resveratrol at the doses of 500 mg/kg, 1000 mg/kg and 1500 mg/kg. Resveratrol induced implanted tumor cells to undergo apoptosis by down-regulation of the apoptosis-regulated gene bcl-2 and up-regulation of the apoptosis-regulated gene bax. Table 1 summarizes the principal effects of resveratrol treatment on gastric cancer.

USE OF RESVERATROL AS A NUTRACEUTICAL IN HUMANS: A CHALLENGE AGAINST ITS POOR BIOAVAILABILITY

Although the use of resveratrol in cell culture models has demonstrated much potential, there has been substantial concern that the concentrations used *in vitro* and in animal models are not reasonably attainable in humans[58]. There is little data regarding the bioavailability of resveratrol in humans. Early research suggested that resveratrol bioavailability was rather limited, considerably less than 1%[59-61] despite a high absorption of almost 70% due to its rapid and extensive metabolism[62]. The metabolism of resveratrol involves both glucuronidation and sulfation in the intestine and liver[63,64]. One of the initial human studies of the absorption and bioavailability uses a single 25 mg oral dose[65], which corresponds to a moderate intake of red wine. After this dose to healthy human subjects, the compound appears in serum and urine predominantly as glucuronide and sulfate conjugates and reaches peak concentrations (10-40 nmol/L) in serum around 30 min after consumption[65]. Sulfate conjugation occurs very rapidly and could be the primary metabolic pathway[66].

Numerous strategies have been developed to enhance the bioavailability of orally administered resveratrol, as recently reviewed[67]. Most of these are based on increasing resveratrol absorption and on protecting resveratrol from its rapid metabolization in the gastrointestinal tract. Resveratrol administration combined with red wine polyphenols could be a simple approach to improving bioavailability, in accordance with the "French Paradox". Indeed, these polyphenols could target the key enzymes that conjugate resveratrol reducing the rate of transformation of trans-resveratrol[68,69]. While piperine, a polyphenol

found in black pepper, enhances the pharmacokinetics of resveratrol by inhibiting its glucuronidation[70], quercetin, found in many fruits, vegetables, leaves and grains, inhibits the human liver sulfotransferase SULT1A1 and thereby reduces the rate of resveratrol sulfate formation[71]. Although research into cellular and animal models has shown that these polyphenols enhance the effects of resveratrol[64,68,72], the co-administration in humans did not increase resveratrol bioavailability[73]. An approach aimed at improving resveratrol absorption is to decrease the particle size of resveratrol by micronization, thus increasing its rate of dissolution and absorption. The micronized resveratrol formulation SRT501 resulted in increased plasma levels and time of maximum plasma concentrations in patients of a phase I trial[74]. Prodrugs may provide another interesting solution that would allow a physiologically significant concentration without toxicity. The acetylation of three hydroxyl groups of resveratrol to obtain 3,5,4'-Tri-O-acetylresveratrol (taRES), a prodrug of resveratrol, masks its principal sites of glucoronidation and sulfation until it is deacetylated to produce resveratrol[75,76]. Intragastric administration of taRES to rats resulted in a greater concentration than those obtained with the equivalent dosage of de-acetylated resveratrol[75]. Pharmacokinetic studies of synthesized carbamate ester derivatives of resveratrol revealed a high water solubility while maintaining to some degree the ability to permeate biomembranes and confirmed absorption after oral administration in rats[77]. In a neuroblastoma cellular model, resveratrol lipoconjugates through phosphate bridges showed significantly more activity than unconjugated resveratrol[78]. In addition to these strategies, recent data has revealed that resveratrol nanoformulations can improve resveratrol transport across the membranes[79], protect resveratrol from metabolism in animal models[80,81], as well as reduce gastrointestinal damages in rats[81] suggesting a possible greater tolerability in humans.

Recently human pilot studies in patients with colorectal and hepatic cancers have confirmed resveratrol beneficial effects in reducing cancer cell proliferation[82], in modulating the expression of some genes of the WNT pathway[83] and in increasing markers of apoptosis in the malignant tissues[74]. Although the bioavailability is very low, rapid uptake and accumulation of resveratrol in epithelial cells along the aerodigestive tract[59] and potentially active resveratrol metabolites may still produce cancer-inhibitory effects in organs like the esophagus and the stomach.

CONCLUSION

GC is closely related to lifestyle factors, especially diet and/or infection by *H. pylori*. Polyphenolic compounds exert an antioxidant protective action against GC. In addition, the consequent anti-inflammatory properties and the ability to inhibit *H. pylori* growth as well as high rate proliferation of GC cells make resveratrol an attractive candidate for GC prevention and therapy. Extremely rapid metabolism appears to be the rate-limiting step in resveratrol bioavailability; however, if sustained resveratrol levels can be achieved in the gastrointestinal tract, there is evidence of a powerful antitumoral effect. It should be noted that, whereas high concentration of the compound result in toxic and pro-apoptotic effects, a fine modulation of resveratrol administration, *i.e.*, by dietary intake and in consideration of its uptake/metabolism, may activate multiple mechanisms such as dihydroceramide-mediated autophagy and epigenetic control of cell cycle/senescence. Most of these mechanisms are deregulated in cancer, thus making this polyphenol a good adjuvant for antitumoral therapies, specifically targeting hyperproliferative cells.

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P- Reviewer: Natsugoe S, Park WS **S- Editor**: Ma YJ **L- Editor**: A
E- Editor: Wang CH

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ISSN 1007-9327