


REVIEW

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A systematic review of the therapeutic effects of resveratrol in combination with 5-fluorouracil during colorectal cancer treatment: with a special focus on the oxidant, apoptotic, and anti-inflammatory activities

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Abstract

Purpose: 5-fluorouracil (5-FU), an effective chemotherapy drug, is commonly applied for colorectal cancer treatment. Nevertheless, its toxicity to normal tissues and the development of tumor resistance are the main obstacles to successful cancer chemotherapy and hence, its clinical application is limited. The use of resveratrol can increase 5-FU-induced cytotoxicity and mitigate the unwanted adverse effects. This study aimed to review the potential therapeutic effects of resveratrol in combination with 5-FU against colorectal cancer.

Methods: According to the PRISMA guideline, a comprehensive systematic search was carried out for the identification of relevant literature in four electronic databases of PubMed, Web of Science, Embase, and Scopus up to May 2021 using a pre-defined set of keywords in their titles and abstracts. We screened 282 studies in accordance with our inclusion and exclusion criteria. Thirteen articles were finally included in this systematic review.

Results: The in vitro findings showed that proliferation inhibition of colorectal cancer cells in the groups treated by 5-FU was remarkably higher than the untreated groups and the co-administration of resveratrol remarkably increased cytotoxicity induced by 5-FU. The in vivo results demonstrated a decrease in tumor growth of mice treated by 5-FU than the untreated group and a dramatic decrease was observed following combined treatment of resveratrol and 5-FU. It was also found that 5-FU alone and combined with resveratrol could regulate the cell cycle profile of colorectal cancer cells. Moreover, this chemotherapeutic agent induced the biochemical and histopathological changes in the cancerous cells/tissues and these alterations were synergized by resveratrol co-administration (for most of the cases), except for the inflammatory mediators.

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Conclusion: The results obtained from this systematic review demonstrated that co-administration of resveratrol could sensitize the colorectal cancer cells to 5-FU treatment via various mechanisms, including regulation of cell cycle distribution, oxidant, apoptosis, anti-inflammatory effects.

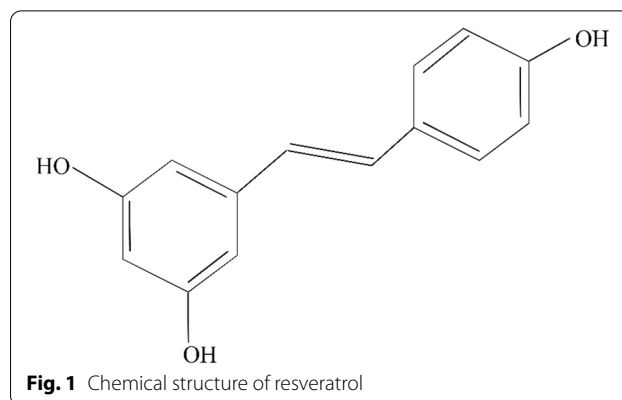
Keywords: Colorectal cancer, Chemotherapy, 5-fluorouracil, Resveratrol, Systemic review

Introduction

Colorectal cancer is the third and second most frequently diagnosed cancer among males and females worldwide, respectively [1]. Furthermore, it is the second most lethal malignancy worldwide [2]. Colorectal cancer is affected by both different genetic and environmental factors, each to a different degree in various patients [3]. The choice of first-line treatment for colorectal cancer patients currently comprises a multimodal approach based on cancer-related features and patient-related factors [4].

One of the therapeutic modalities for colorectal cancer is using different chemotherapy regimens; especially, it is considered as the mainstay of treatment in metastatic colorectal cancer. There are various chemotherapeutic drugs for managing colorectal cancer patients, including 5-fluorouracil (5-FU), capecitabine, oxaliplatin, cetuximab, irinotecan, bevacizumab, etc. [5, 6]. 5-FU is a common and conventional treatment for colorectal cancer which is used for five decades. Nevertheless, its toxicity to normal tissues and appearance of colorectal cancer chemoresistance are main obstacles to successful cancer chemotherapy and hence, its clinical application is limited [7, 8]. Therefore, identification of new therapeutic agents for their potential application combined with 5-FU during colorectal cancer treatment is warranted to improve patient survival and alleviate adverse effects.

The tendency to use herbal and natural products or their derivatives to mitigate the chemotherapy-induced side effects (chemo-protectors) or enhance the sensitivity of tumoral cells to chemotherapeutic agents (chemo-sensitizers) has attracted much attention during the past several decades. Resveratrol (3,5,4'-trihydroxy-trans-stilbene, Fig. 1) is a natural polyphenol which has been found in more than 70 plant species and its main sources are grapes, soy and peanuts [9–13]. Resveratrol is naturally able to protect herbs against fungal, ultra-violet rays, and other stresses [14]. It is also known that this herbal agent has potent anti-oxidant and anti-clastogenic properties, helping to protect against carcinogenesis and genomic instability [15, 16]. Moreover, its anti-cancer activity has been investigated in many cancer types, such as colorectal, prostate, lung, liver, breast cancers, and so on [17–21]. It has been also reported that resveratrol not only acts a chemotherapeutic agent, but also have chemo-preventive properties which are related to its anti-inflammatory, anti-oxidant, anti-apoptosis, and anti-proliferative activities



[22–24]. Indeed, resveratrol targets some components of intracellular signaling pathways such as tumor angiogenic and metastatic switches, pro-inflammatory mediators, and cell survival and apoptosis regulators by modulating a distinct set of transcription factors (including p53, aryl hydrocarbon receptor, nuclear factor-erythroid 2-related factor 2 (Nrf2), forkhead box subgroup O, activating transcription factor 3, nuclear factor kappa B (NF- κ B), etc.), upstream kinases (including mitogen-activated protein kinases (MAPKs), protein kinase C, and Akt, etc.) and their regulators (including early growth response-1, Krüppel-like factor-4, I κ B α kinase (IKK), cyclooxygenase (COX)-2, vascular endothelial growth factor (VEGF), Bcl2, matrix metalloproteinase (MMP)-9, etc.) [25–29].

In the current study, a systematic search was carried out on the potential therapeutic role of resveratrol during colorectal cancer chemotherapy by 5-FU. Additionally, we tried to answer the following issues: (1) the underlying mechanisms of toxicities induced by 5-FU chemotherapeutic agent on colorectal cancer cells, (2) the role of resveratrol on 5-FU-induced toxicities on colorectal cancer cells, and (3) the underlying mechanisms related to the chemo-sensitization role of resveratrol on colorectal cancer cells during 5-FU chemotherapy.

Methods

Search strategy

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [30], we performed a systematic search to assess all relevant studies on “the effects of resveratrol in combination

with 5-FU against colorectal cancer” in both medical subject heading (MeSH) or advance at four electronic databases including Web of Science, Embase, PubMed, and Scopus up to May 2021 using the keywords “Resveratrol” AND “Chemotherapy” OR “5-Fluorouracil” OR “5Fluorouracil” OR “5-FU” OR “5FU” OR “Fluorouracil” OR “Aducil” OR “Carac” AND “Colorectal cancer” OR “Bowel cancer” OR “Colon cancer” OR “Rectal cancer” OR “Rectum cancer” OR “Colorectal malignancy” OR “Bowel malignancy” OR “Colon malignancy” OR “Rectal malignancy” OR “Rectum malignancy” OR “Colorectal neoplasm” OR “Bowel neoplasm” OR “Colon neoplasm” OR “Rectal neoplasm” OR “Rectum neoplasm” OR “Colorectal carcinoma” OR “Bowel carcinoma” OR “Colon carcinoma” OR “Rectal carcinoma” OR “Rectum carcinoma” OR “Colorectal tumor” OR “Bowel tumor” OR “Colon tumor” OR “Rectal tumor” OR “Rectum tumor” in keywords, titles or abstracts.

Study selection

The inclusion criteria considered for this systematic review were full-text articles with (1) English language, (2) our per-defined purpose on the role of resveratrol during colorectal cancer chemotherapy by 5-FU (based on the aforementioned keywords), (3) sufficient information, (4) no restriction on publication year, and (5) no restriction in publications with clinical, in-vivo, or in-vitro studies. For exclusion criteria, we excluded (1) not related papers, (2) review articles, (3) oral presentations, (4) posters, (5) case reports, (6) editorials, (7) letters to the editors, and (8) book chapters.

Data extraction

Each eligible study was reviewed by two researchers and the following data were then extracted: (a) author name and year of publication, (b) models (clinical, in-vivo or/and in-vitro), (c), 5-FU dosage and route of administration type, (d) outcomes of colorectal cancer chemotherapy, (e) resveratrol dosage and route of administration type, and (f) resveratrol co-administration outcomes.

Results

Literature search and screening

Figure 2 shows the process of study selection.

Two hundred and eighty-two articles were acquired by a comprehensive search on Web of Science ($n = 112$), Embase ($n = 56$), PubMed ($n = 60$), and Scopus ($n = 54$) electronic databases up to May 2021. After removing the duplicated papers ($n = 155$), the remaining ones ($n = 127$) were screened in their titles and abstracts, and 96 of them were omitted. Thirty-one articles were qualified for assessment of their full-texts. Thirteen articles were included in the current systematic review in accordance

with the inclusion and exclusion criteria. The data of each eligible article were extracted and listed in Table 1.

The effects of resveratrol in combination with 5-fluorouracil against colorectal cancer Cell proliferation inhibition

The results obtained from some studies showed that proliferation inhibition of colorectal cancer cells in the groups treated by 5-FU was remarkably higher than the untreated groups [31–38]. Additionally, the inhibited cell proliferation following 5-FU treatment had time- and dose-dependent manners. In detail, it was observed that the colorectal cancer cell viability increases over time; while, the colorectal cancer cell viability decreases by increasing the chemotherapy dosage [31, 33, 35, 37, 38]. Furthermore, the type of colorectal cancer cell had a considerable effect on 5-FU-induced cell growth inhibition. For instance, it was shown that the SW-620 cells were more resistant to 5-FU than the HT-29 cells [33]. In addition, it was reported that the parental colorectal cancer cells (such as HCT116 and SW480) were more sensitive to 5-FU treatment than their corresponding isogenic FU-chemoresistant derived clones (i.e., HCT116R and SW480R) [35]. The resveratrol co-administration significantly increased cytotoxicity induced by 5-FU treatment on the colorectal cancer cells (synergistic effect) [31–38].

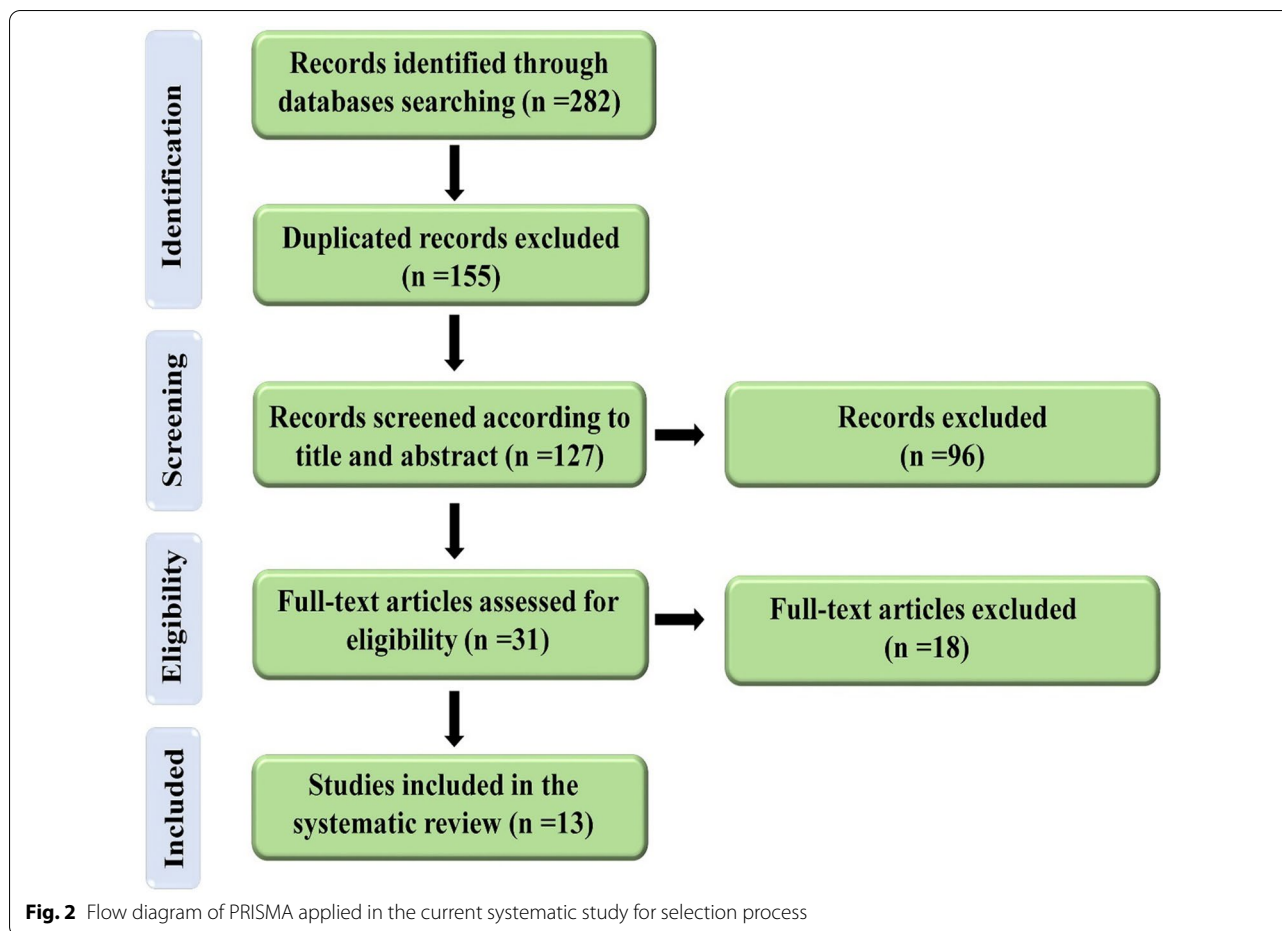
Tumor volume and tumor weight changes

The in vivo results demonstrated that tumor volume and tumor weight of mice were decreased in the 5-FU group than the untreated group. When both resveratrol and 5-FU were administered to the mice, dramatic decreases in the tumor volume and tumor weight were found compared to the 5-FU-treated group [39].

Cell cycle distribution

The findings revealed that the use of 5-FU chemotherapeutic agent regulated the cell cycle profile of colorectal cancer cells [32, 37, 40]. Chung et al. showed that upon 5-FU treatment, the HCT116 cells (%) in G_0/G_1 phase decreased, while the rate of these cells in S phase increased compared to the control group [37]. The combined treatment of resveratrol and 5-FU had a reverse manner on the cell cycle distribution compared with the chemotherapy group alone [37]. However, Mohapatra et al. showed that treatment with 5-FU alone and combined with resveratrol halted the cell cycle progression at the S phase in the HCT-116 cells [32].

It is noteworthy that the effect of combined treatment of 5-FU and resveratrol (compared with 5-FU alone) on the cell cycle distribution depends on the type of colorectal cancer cell and can provide different results.



Changes induced in biochemical markers

The biochemical changes induced by 5-FU treatment on colorectal cancer cells/tissues are listed in Table 1. It was found that intracellular reactive oxygen species (ROS), lipid peroxidation (LPO), malondialdehyde (MDA), superoxide dismutase (SOD), Bcl-2-associated X protein (BAX), CXCR4, MMP-9, cleaved poly (ADP-ribose) polymerase (PARP), phospho-JNK, phospho-p38, vimentin, activated nuclear factor kappa B, I κ B α , IKK, interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF- α) levels increased significantly in the 5-FU-treated groups than the untreated groups [7, 32, 33, 35, 36, 38–41]. In contrast, catalase, glutathione peroxidase (GPx)/SOD ratio, B-cell lymphoma-extra large (Bcl-xL), Bcl-2, phospho-AKT, phospho-signal transducer and activator of transcription 3 (STAT3), phospho-extracellular signal-regulated kinase (ERK)1/2, Sirt1, E-cadherin, claudin-2, aldehyde dehydrogenase isoform 1 (ALDH1), CD31, CD44, CD51, and CD133 levels decreased significantly [7, 32–35, 37, 39, 41].

The combined treatment of resveratrol and 5-FU synergized biochemical changes induced by 5-FU treatment

alone (for most of the cases) [32–34, 36–41]. Nevertheless, it was observed that combination treatment of resveratrol and 5-FU compared to chemotherapy alone had a reverse manner on several biochemical markers (for instance, MDA, SOD, CXCR4, MMP-9, activated NF- κ B, I κ B α , IKK, vimentin, E-cadherin, claudin-2, IL-6, and TNF- α) [7, 35, 39, 41].

It is noteworthy that several studies have shown conflicting results on several biochemical markers (see Table 1). For instance, several studies showed decreased levels of cleaved caspase-3, P53 gene, transcription factor slug, and COX-2 following 5-FU treatment alone [7, 35, 37, 38], while other studies revealed increased levels for these biomarkers [32, 35, 38–40]. Nevertheless, the combined treatment of resveratrol and 5-FU increased the cleaved caspase-3 and P53 gene levels and decreased the transcription factor slug and COX-2 levels, compared with chemotherapy groups alone [7, 32, 35, 37–41].

Histological changes

The histopathological results from the colon tissues of rats which received methylnitrosourea (as a tumor

Table 1 The characteristics of included studies

Author & year	Model	5-FU dosage & protocol of usage; route of administration	Outcomes of 5-FU chemotherapy drug	Resveratrol dosage & protocol of usage; route of administration	Resveratrol co-administration outcomes
Colin et al., 2009 [31]	In vitro/SW480 cells	1, 2, 5, and 10 μM & 24 h	↑ cell proliferation inhibition	10 μM & co-treatment and 24 h prior to treatment	↑↑ cell proliferation inhibition
Lee et al., 2010 [115]	In vitro/HCT116 cells	50 μM & 24 h	No change in caspase-6 level	200 μM & 24 h after treatment	↑ caspase-6 activation
Mohapatra et al., 2011 [32]	In vitro/HCT116 cells	0.2, 0.5, 1.0, 2.0, 2.5, 5.0, and 10.0 μM & 24 h	↓ cell survival, ↓ cell migration, ↑ apoptosis, ↑ BAX, ↓ Bcl-XL, ↑ cleaved caspase-3, caspase-8, & caspase-9, ↑ cleaved PARP, ↑ cell population (%) in S phase, ↑ DNA damage, ↑ phospho-JNK & phospho-p38 levels	5, 10, 15, and 20 μM & 24 h prior to treatment	↓ cell survival, ↓ migration, ↑↑ apoptosis, ↑↑ BAX, ↓↓ Bcl-XL, ↑↑ cleaved caspase-3, caspase-8, & caspase-9, ↑↑ cleaved PARP, ↑↑ cell population (%) in S phase, ↑↑ DNA damage, ↑↑ phospho-JNK & phospho-p38 levels
Santandreu et al., 2011 [33]	In vitro/HT-29 & SW-620 cells	10 μM & 6 h	↓ cell viability in HT-29 cells, ↑ intracellular ROS & LPO, ↓ catalase & GPx/SOD ratio, ↓ phospho-AKT & phospho-STAT3	100 μM & co-treatment	↓ cell viability in both HT-29 & SW-620 cells, ↑↑ intracellular ROS & LPO, ↓↓ catalase & GPx/SOD ratio, ↓↓ phospho-AKT & phospho-STAT3
Hotmog et al., 2013 [40]	In vitro/LoVo cells	25 μM & 24 h and 72 h	↑ apoptosis (for both 24 h & 72 h treatment), ↑ cell population (%) in G ₀ /G ₁ phase, ↓ cell population (%) in S phase, ↑ P53 & BAX expression, ↓ Bcl-2 expression	25, 50 and 100 μM & 6 h prior to treatment	↑↑ apoptosis (for 24 h treatment) & ↓ apoptosis (for 48 h treatment), ↑↑ cell population (%) in G ₀ /G ₁ phase (for 25 μM resveratrol + 25 μM 5-FU) & ↓ cell population (%) in G ₀ /G ₁ phase (for 100 μM resveratrol + 25 μM 5-FU), ↓↓ cell population (%) in S phase, ↑↑ P53 & BAX expression, ↓↓ Bcl-2 expression
Kumazaki et al., 2013 [34]	In vitro/DLD-1, SW480 & COLO201 cells	1 μM & NI	↓ cell viability, ↓ phospho-Erk1/2, Erk1/2 & Sirt1 levels	10 μM & NI	↓ cell viability, ↓↓ phospho-Erk1/2, Erk1/2 & Sirt1 levels

Table 1 (continued)

Author & year	Model	5-FU dosage & protocol of usage; route of administration	Outcomes of 5-FU chemotherapy drug	Resveratrol dosage & protocol of usage; route of administration	Resveratrol co-administration outcomes
Buhrmann et al., 2015 [35]	In vitro/HCT116, SW480, HCT116 ^R & W480 ^R cells	0.01, 0.1, and 1 nM & 1–22 days	↓proliferation of HCT116 cells, ↓migration rate of HCT116 cells, ↓number of intercellular junctions in both HCT116 & HCT116 ^R cells, ↑apoptosis in HCT116 cells, ↓E-cadherin & claudin-2 proteins in both HCT116 & HCT116 ^R cells, ↑vimentin & transcription factor Slug expression in both HCT116 & HCT116 ^R cells, ↑NF-κB & IκBα phosphorylation in both HCT116 & HCT116 ^R cells, ↑activation of IKK, ↑MMP-9 & ↓cleaved caspase-3 in both HCT116 & HCT116 ^R cells	5 μM & co-treatment	↓proliferation of HCT116 & HCT116 ^R cells, ↓migration rate of HCT116 & HCT116 ^R cells, ↑number of intercellular junctions in both HCT116 & HCT116 ^R cells, ↑apoptosis in both HCT116 & HCT116 ^R cells, ↑E-cadherin & claudin-2 proteins in both HCT116 & HCT116 ^R cells, ↓vimentin & transcription factor Slug expression in both HCT116 & HCT116 ^R cells, ↓NF-κB & IκBα phosphorylation in both HCT116 & HCT116 ^R cells, ↓activation of IKK, ↓MMP-9 & ↑cleaved caspase-3 in both HCT116 & HCT116 ^R cells
Blanquer-Rossello et al., 2017 [36]	In vitro/SW620 cells	10 μM & NI	↑ROS, ↓cell viability	10 μM & NI	↑↑ROS, ↓↓cell viability
Buhrmann et al., 2018 [41]	In vitro/HCT116 & HCT116 ^R cells	0.1 and 1 nM & 10 days	↓invasion ability of HCT116 cells, ↓CD133, CD44 & ALDH1 in HCT116 cells, ↑apoptosis in HCT116 cells, ↑NF-κB activation, ↑MMP-9 & CXCR4 levels in HCT116 cells	5 μM; co-treatment	↓invasion ability of HCT116 & HCT116 ^R cells, ↓CD133, CD44 & ALDH1 in both HCT116 & HCT116 ^R cells, ↑apoptosis in both HCT116 & HCT116 ^R cells, ↓NF-κB activation, MMP-9 & CXCR4 levels in both HCT116 & HCT116 ^R cells, ↑cleaved caspase-3 in both HCT116 & HCT116 ^R cells, ↑E-cadherin, ↓vimentin & transcription factor slug in both HCT116 & HCT116 ^R cells

Table 1 (continued)

Author & year	Model	5-FU dosage & protocol of usage; route of administration	Outcomes of 5-FU chemotherapy drug	Resveratrol dosage & protocol of usage; route of administration	Resveratrol co-administration outcomes
Chung et al., 2018 [37]	In vitro/DLD1 & HCT116 cells	10 μM & 24 h and 72 h	↓cell proliferation, ↓population of HCT 116 cells (%) in G ₀ /G ₁ phase, ↑population of HCT 116 cells (%) in S phase, ↑apoptosis in HCT 116 cells, ↓apoptosis in DLD1 cells, ↓transcription factor slug in both DLD1 & HCT116 cells, ↓CD51 in both DLD1 & HCT116 cells, ↓CD44 in HCT116 cells, ↓phospho-STAT3 & phospho-AKT in both DLD1 & HCT116 cells, ↓STAT3 binding to hTERT promoter region & telomerase activity in both DLD1 & HCT116 cells	25 μM & co-treatment	↑cytotoxicity, ↑population of HCT 116 cells in G ₀ /G ₁ phase, ↓population of HCT 116 cells in S phase, ↓population of DLD1 cells in G ₀ /G ₁ phase, ↑population of DLD1 cells in S phase, ↑apoptosis in both DLD1 & HCT116 cells, ↓↓ vimentin & transcription factor slug in HCT116 cells, ↓migration capacity (↑gap size) in both DLD1 & HCT116 cells, ↓↓ CD51 & CD44 in both DLD1 & HCT116 cells, ↓↓phospho-STAT3 & phospho-AKT in both DLD1 & HCT116 cells, ↓↓STAT3 binding to hTERT promoter region & telomerase activity in both DLD1 & HCT116 cells
Latif et al., 2019 [7]	In vivo/rats	12.5 mg/kg/day & on days 1, 3, and 5 with the cycle being repeated every 4 weeks over the duration of 4 months; <i>i.p</i>	↑MDA & AOPP, ↓SOD, ↑plasma NF-κB, ↓P53 expression, ↓COX-1 & COX-2 expression	10 mg/kg/day & co-treatment; oral	↓MDA & AOPP, ↑SOD, ↓plasma NF-κB, ↑P53 expression, ↓↓COX-1 & COX-2 expression
Hu et al., 2019 [39]	In vivo/mice	30 mg/kg/2 days & for 30 days; <i>i.p</i>	↓body weight, tumor volume & tumor weight, ↑inhibition rate, ↓vascular density, ↓CD31 & phospho-ERK, ↑COX-2 expression, ↑IL-6 & TNF-α levels	1920 mg/kg/day & co-treatment; <i>i.g</i>	↓↓body weight, tumor volume & tumor weight, ↑↑inhibition rate, ↓↓vascular density, ↓↓CD31 & phospho-ERK, ↓COX-2 expression, ↓IL-6 & TNF-α levels
Huang et al., 2019 [38]	In vitro/SW480, SW480 tumorigenic stem cells (SW480 CD133 ⁺), LoVo & LoVo tumorigenic stem cells (LoVo CD133 ⁺)	10, 20, 40, 80, 160, and 320 μM & 24 h	↓cell survival rate, ↓caspase-3, ↑P53 & BAX expression	80, 160, & 320 μM & co-treatment	↓↓cell survival rate, ↑caspase-3, ↑↑P53 & BAX expression

↑ Increase; ↓ Decrease; NI, Not informed; *i.p.*, Intraperitoneal; *i.g.*, Intragastral; MDA, Malondialdehyde; ROS, Reactive oxygen; GPx, Glutathione peroxidase; SOD, Superoxide dismutase; JNK, c-Jun N-terminal kinase; COX, Cyclooxygenase; LPO, Lipid peroxidation; MMP-9, matrix metalloproteinase-9; PARR, Poly (ADP-ribose) polymerase; IKK, IκB kinase; AOPP, advanced oxidation protein products; BAX, Bcl-2-associated X protein; Bcl-xL, B-cell lymphoma-extra large; STAT3, Signal transducer and activator of transcription 3; ERK1/2, Extracellular signal-regulated kinase 1/2; NF-κB, Nuclear factor kappa B; ALDH1, Aldehyde Dehydrogenase 1; IL-6, Interleukin 6; TNF-α, Tumor necrosis factor alpha

inducer) demonstrated moderate to severe inflammation, epithelial hyperplasia determined by crypt injury, and inflammatory cell infiltration. Nevertheless, the colon tissue sections from methylnitrosourea-induced colon cancer rats treated with 5-FU alone and 5-FU combined with resveratrol had more intact surface epithelium, less inflammatory, and normal colon cells than the methylnitrosourea-induced colon cancer group [7]. In another study, the histopathological findings obtained from mice with untreated colon tumors revealed blood vessels with a high vascular density; nevertheless, the vascular network of 5-FU-treated group illustrated significantly lower vascular density and branches and this decreased vascular density was severe in the group treated with resveratrol and 5-FU [39].

Discussion

In the current systematic review, we aimed to investigate the cytotoxic effects induced by 5-FU treatment on colorectal cancer cells/tissues. Additionally, the potential therapeutic effects of resveratrol in combined with 5-FU were assessed. A summary of the results has been presented in Table 1. Moreover, the effects of resveratrol co-treatment during colorectal cancer treatment by 5-FU chemotherapeutic agent are depicted in Fig. 3.

Chemotherapy drugs is widely applied to treat different malignant tumors, such as head and neck, breast, gastric, and colorectal, etc. [42–45]. These drugs are able to modulate cell cycle that results in apoptosis [46–48]. The treatment of colorectal cancer with 5-FU (especially advanced cases) has two major problems: severe toxicity

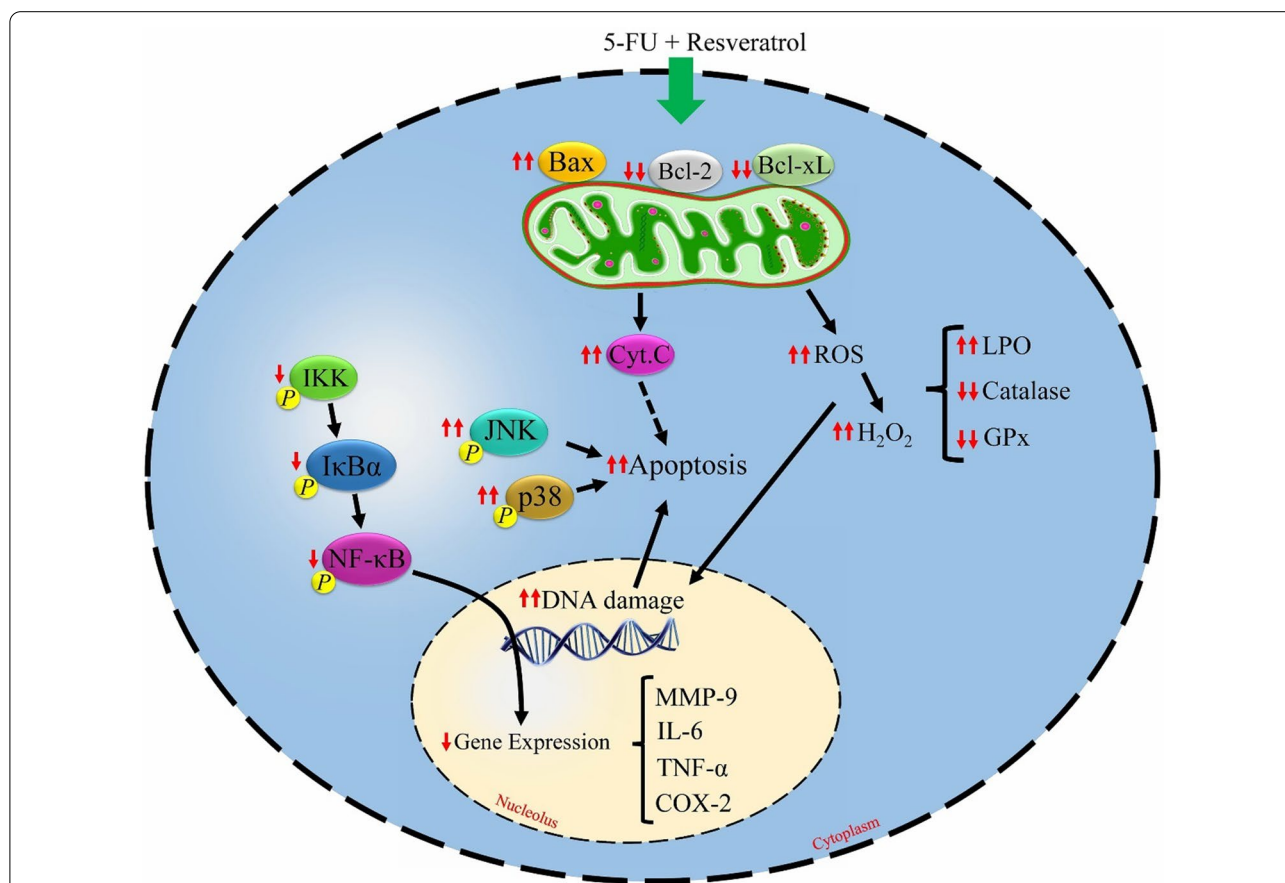


Fig. 3 The molecular mechanisms of resveratrol co-treatment during colorectal cancer treatment by 5-fluorouracil (5-FU) chemotherapeutic agent. Resveratrol exerts the synergistic anti-tumoral effects through increments in oxidant and apoptosis activities, and reduction in inflammatory effects. ↑↑synergistically increased by 5-FU plus resveratrol compared to 5-FU alone; ↑↑synergistically decreased by 5-FU plus resveratrol compared to 5-FU alone; ↓decreased by 5-FU plus resveratrol compared to 5-FU alone; Bcl-xL, B-cell lymphoma-extra large; BAX, Bcl-2-associated X protein; GPx, glutathione peroxidase; IL-6, interleukin 6; IKK, IκBa kinase; LPO, lipid peroxidation; ROS, reactive oxygen species; NF-κB, nuclear factor-kappa B; COX-2, cyclooxygenase-2; TNF-α, tumor necrosis factor alpha; MMP-9, matrix metalloproteinase-9

to normal tissues and development of tumor resistance [33]. As its dose increases, the unwanted adverse effects of the chemotherapeutic agent also increase and resistance to the agent develops frequently [8]. In addition, concomitant use of other chemotherapy drugs with 5-FU in colon cancer patients with advanced stages develops drug resistance against chemotherapy and these patients suffer from severe adverse effects [49, 50]. In view of the above, clinical application of 5-FU is limited during colorectal cancer treatment. These limitations highlight the requirement for the development of novel anti-tumoral agents in order to enhance the chemosensitivity of colorectal cancer cells and reduce unwanted adverse effects. In this regard, the combination treatment of 5-FU with less toxic substances derived from plants, such as resveratrol, has received more attention in recent years.

The anti-tumoral activity of resveratrol has been reported in some cancers, such as breast [51], skin [52], gastric [53], liver, and colorectal [54] cancers. More importantly, it has been shown that a combination of resveratrol and chemotherapeutic drugs not only can mitigate adverse drug reactions but can also reduce drug resistance (synergistic effect) [38, 55, 56]. Resveratrol exerts its anti-tumoral effects through several mechanisms, including oxidant, apoptotic, anti-inflammatory actions, etc. In the following, the mechanistic effects of 5-FU treatment on the colorectal cancer cells/tissues as well as the anti-tumoral effects of resveratrol co-treatment during colorectal cancer treatment by 5-FU chemotherapeutic agent are discussed.

Oxidant actions

Free radicals are normally generated in the cells and several defense mechanisms protect the cells against them [57, 58]. In oxidative stress conditions, a lack of balance between the free radical amounts and these defense systems occurs, leading to increased free radical amounts [59, 60]. Following the chemotherapy drug administration, the oxidative stress condition happens [61]. The generated ROS following 5-FU treatment can induce DNA damage either directly or indirectly, leading to cancerous cell death [33, 36, 62]. It was also showed that LPO levels were increased in both the plasma and erythrocyte samples of 5-FU-treated colorectal cancer patients, whereas GPx and glutathione (GSH) levels were decreased [63]. Additionally, 5-FU significantly inhibited the catalase activity and increased SOD activity [33]. These findings reflect that 5-FU treatment impairs hydroperoxide scavenging capacity in colon cancer cells. It is noteworthy that non-radical ROS such as H_2O_2 through the activity of GPx enzyme and consuming GSH (as an important intracellular anti-oxidant agent) generates $2H_2O$ [64]. Additionally, the catalase enzyme decomposes H_2O_2 to H_2O

and O_2 [65]. $O_2^{\cdot-}$ also is one of the ROS molecules and it is turned to H_2O_2 by the SOD enzyme [66]. Moreover, the marked increases in advanced oxidation protein products and MDA levels of 5-FU-treated colon cancer rats were observed [7]. In contrast, the colorectal cancer cell lines resistant to 5-FU showed increments in glutathione transferases (GST) level and Nrf2 expression following 5-FU treatment [67, 68]. The activated Nrf2 also led to an increment in the protein expression and activity of heme oxygenase-1 (HO-1) [68]. Nrf2 is a transcription factor for several molecules involved in anti-oxidant activities, including NAD(P)H Quinone Dehydrogenase 1, HO-1, GST, and γ -glutamylcysteine synthetase (γ -GCS) [69]. Hence, an increased Nrf2 expression or Nrf2-regulated cytoprotective genes (such as GST) may play an important role in 5-FU resistance of cancerous cells.

Resveratrol through oxidant actions increased ROS level in colorectal cancer cells [33, 36]. It has been also shown that this herbal agent through the interaction with the mitochondria of malignant cells is able to induce an imbalance in cellular anti-oxidant activities, which results to a remarkable increment in the levels of both intracellular ROS and lipid peroxides [33]. It is noteworthy that free radicals are normally created in the cells, particularly through electrons leakage from the mitochondrial electron transport chain and this process is enhanced during mitochondria damage [70]. Resveratrol can also inhibit oxidation–reduction (redox) system in malignant cells [33]. Moreover, it can downregulate catalase and GPx expressions and upregulate MDA, SOD, and LPO levels in colorectal cancer cells [7, 33]. Resveratrol can also suppress Nrf2 activity, which may sensitize cancer cells resistance to chemotherapy agents in this way [71]. Besides, it was found that resveratrol combined with 5-FU chemotherapeutic drug against colorectal cancer synergistically increased the generated ROS, LPO, and SOD levels and decreased the catalase and GPx levels [33, 36].

Apoptotic actions

Apoptosis is a physiological pathway which is needed to eliminate the harmed or transformed cells [72, 73]. It can happen during oxidative stress conditions and enormous DNA damage [74, 75]. Among the important mediators involved in the apoptosis process are caspase enzymes, Bcl-2, p53, BAX, Bcl-XL, ceramide, PARP, nuclear factor of activated T cells 5 (NFAT5), and so on [76–87]. One of the characteristics of most cancerous cells is the evasion of apoptosis; as any reduction or irregularity of this pathway invariably accompanies tumorigenesis and maintains malignant progression [88]. Some chemotherapeutic agents are able to induce apoptosis in tumoral cells [89, 90]. Several studies have reported an increased apoptosis level in 5-FU-treated

colorectal cancer cells than untreated groups [32, 35, 41]. When colorectal cancer cells were treated to 5-FU, Bcl-XL expression was decreased compared to the untreated group [32]. In contrast, it was found that BAX, cleaved caspase-3, caspase-8, caspase-9, and PARP product levels were increased following 5-FU treatment [32, 38]. p53, tumor suppressor protein, has pro-apoptotic activities and 50–70% of colorectal tumors contain p53 mutation [91]. It was shown an increased level of P53 expression following 5-FU treatment [92]. These indicate that colorectal cancer cells are moving towards apoptosis. PARP is a nuclear enzyme and, as a pro-apoptotic factor, can be activated by chemotherapeutic agents [32, 93–95]. It has been also reported that 5-FU damages DNA and takes the colon cancer cells to apoptosis by activating the MAPK pathway [96]. In this regard, it was found that 5-FU activates (phosphorylates) phospho-JNK and phospho-p38 (major MAPK signaling components) [32]. MAPKs may also affect NFAT5 [97–100] and p53 [101] activities. NFAT5 is a transcription factor which plays a critical role in apoptosis [86]. Moreover, it was shown that 5-FU induces apoptosis through suppression of the MAPK/ERK1/2 signaling pathway in colon cancerous cells [34].

Some studies have reported that resveratrol can induce apoptosis in various malignant tumor cells, such as glioma [102], prostate [103], gastric [104], breast [105], head and neck [106], and ovarian [107] cancer cells. The apoptotic activation of resveratrol is linked to induce ROS production, various caspases activation, mitochondrial membrane permeability, BAX and p53 activation, etc. [108–113]. It has been reported that colorectal cancer cells treated with resveratrol revealed an increased apoptosis level compared to untreated groups [32, 35, 114, 115]. The use of resveratrol decreased Bcl-XL expression in the cancerous cells, while it led to increased levels of BAX, cleaved caspase-3, caspase-6, caspase-8, caspase-9, and PARP product [32, 35, 38]. It was also result to increase p53, phospho-JNK, and phospho-p38 levels in colorectal cancer cells [7, 32, 38]. Additionally, resveratrol suppressed the MAPK/ERK1/2 signaling pathway in colon cancerous cells, leading to increase apoptosis [34]. Moreover, the results represented in this study showed that the use of resveratrol could synergize 5-FU-induced apoptosis in colorectal cancer cell lines [32, 35, 37].

Inflammatory actions

The inflammatory process is a biological phenomenon which occurs in response to tissue damage induced from several harmful stimuli such as chemotherapy, radiation, microbial pathogen infection, and/or wounding [116–121]. Among the characteristics of inflammation are: elevation in leukocyte migration to injured area,

upregulation of pro-inflammatory cytokines, and leukocyte chemotaxis [122, 123]. The chemotherapy-induced inflammation has a main role in tumor resistance and the incidence of various adverse effects. Additionally, chronic inflammation may develop second cancer during years after treatment [124]. Moreover, inflammatory mediators play an important role in angiogenesis and tumor growth. For instance, NF- κ B is considered as one of the most significant links between inflammation, tumor resistance, and cell death [124]. It was found chemotherapy by 5-FU increases NF- κ B phosphorylation in colorectal cancer cells [7, 35, 41, 124]. In addition, 5-FU markedly induced phosphorylation of I κ B α subunit, expression of MMP-9, and activation of IKK [35, 41, 125]. The MMP-9, as an enzyme involved in the inflammatory pathway, is regulated by NF- κ B [125]. I κ B inhibits nuclear translocation of NF- κ B and also activation of IKK induces phosphorylation of NF- κ B and I κ B [85]. NF- κ B can also stimulate the release of prostaglandins and resistance of cancerous cells to apoptosis through upregulation of COX-2 [124]. The findings obtained from 5-FU-treated mice also showed an increased expression of COX-2 than the control group [39]. COX-2 is a pro-inflammatory enzyme that is overexpressed at the inflammatory site of cancer [126]. It is a marker representing a worse prognosis and a stimulator for various cancers through multitasking roles (recently discussed in detail by Hashemi Goradel et al. [127]). It is noteworthy that suppression of NF- κ B and COX-2 by novel therapeutic agents could provide a promising approach for cancer treatment, particularly when they are applied as an adjuvant with appropriate chemotherapy drugs. It has been also reported that the phosphorylated STAT3 level decreases in response to 5-FU treatment than the control levels of colorectal cancer cells [33, 37]. One of the reasons for the resistance of cancerous cells is the upregulation of transcription factors such as STATs [16]. These enzymes are considered as transcription factors for cytokine signaling which are constitutively activated in many cancer types [128–131]. STAT3, as one of the subfamilies, involves in the modulation of angiogenesis and metastasis, suppression of apoptosis, and regulation of cell cycle progression via stimulation of VEGF, MMP-2, MMP-9, and IAP-1 [16, 132]. Of note, targeting the STATs by chemotherapy agents can be considered as a strategy for overcoming tumor resistance. Moreover, the increased levels of IL-6 and TNF- α following 5-FU-treated colorectal cancer cells have been reported [39].

As mentioned earlier, inflammation is an inducer of carcinogenesis and can significantly affect the therapeutic outcome of chemotherapy [127, 133]. In this regard, resveratrol, through its anti-inflammatory activities, can increase therapeutic efficiency and reduce the resistance

of cancer cells to chemotherapy drugs. According to the findings obtained from combined treatment of resveratrol and 5-FU, it was found that resveratrol reduces phosphorylated NF- κ B, I κ B α , and IKK levels as well as MMP-9, COX-2, IL-6, and TNF- α levels in colorectal cancer cells [7, 35, 39, 41]. Resveratrol also synergistically reduced phosphorylated STAT3 levels in 5-FU-treated colorectal cancer cells [33, 37].

Perspective of future research

In addition to its anti-tumoral effects, resveratrol is able to mitigate chemotherapy-induced toxicities in normal cells/tissues. Resveratrol exerts the chemo-protective effects through anti-oxidant, anti-apoptotic, anti-inflammatory actions. Hence, it is proposed to conduct studies on the chemo-protective effects of resveratrol in normal cells/tissues during colorectal cancer chemotherapy by 5-FU.

It is noteworthy that the results represented in this systematic review are in accordance with in vitro and in vivo models. The use of resveratrol as a chemo-protector agent or/and chemo-sensitizer agent combined to 5-FU in colorectal cancer patients needs further studies because sometimes results are different between the in vitro and in vivo models and clinical studies.

Conclusion

The obtained findings revealed that combined treatment of resveratrol and 5-FU chemotherapeutic drug significantly increases the effectiveness of 5-FU treatment alone in colorectal cancer cells through increment of chemo-sensitizer and/or reduction of chemoresistance effects. Resveratrol, as an anti-tumoral agent, exerts the synergistic effects through various mechanisms such as regulation of cell cycle distribution, increments in oxidant and apoptosis activities, and reduction in inflammatory effects.

Acknowledgements

Not applicable.

Author contributions

HM, MM, and HB gave the idea and drafted the manuscript. RGhA, MY, GhA, and ZF performed the literature search and drafted figures. BF edited the manuscript and supervised the whole study. EGH substantively revised the manuscript. All authors read and approved the final manuscript.

Funding

None.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that there are no conflicts of interest.

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Received: 1 October 2021 Accepted: 27 March 2022

Published online: 02 April 2022

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