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Mini Review

Recent Advances in Anti-Colorectal Cancer Activities of Resveratrol

Chung-Ming Lin[1], Hui-Jye Chen[2,*]

[1] Department of Biotechnology, School of Health and Medical Engineering, Ming Chuan University, Taoyuan 33348, Taiwan

[2] Graduate Institute of Biomedical Sciences, School of Medicine, China Medical University, Taichung 40402, Taiwan

Abstract

Resveratrol is a phytoalexin that harbors many beneficial activities. Resveratrol displays anticancer activity against a variety of cancers, including colorectal cancer. Here we reviewed the latest progress in the effects of resveratrol and resveratrol analogues on colorectal cancer, concentrating on the activities of resveratrol in novel signaling pathways, on anti-colorectal cancer (CRC) activities of newly synthesized compounds, nanoencapsulation and drug combination of resveratrol to increase anti-CRC activities. Finally sophisticated tools including metabolite profiling, bioinformatics, system biology, and computational predication are employed to reveal potential drugs including resveratrol and their drug targets for CRC therapy. We hope that this updated review of resveratrol and resveratrol analogues on CRC can have contribution in future therapeutic application to colorectal cancer and other diseases.

Keyword: resveratrol, colorectal cancer, nanoencapsulation, anti-cancer activity
Corresponding author: Hui-Jye Chen [huijyechen@mail.cmu.edu.tw]
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1. Introduction

Resveratrol (trans-3,4’,5-trihydroxystilbene), a non-flavonoid-polyphenol organic

compound, is found in many plants such as grapes, tea, peanuts and berries [1]. It belongs to the stilbene family, which also include the methoxylated stilbene rhapontigenin and the hydroxylated stilbene resveratrol. Resveratrol possesses many biological function, including cardioprotective, neuroprotective, antioxidant, anti-inflammatory, anti-aging, and anticancer activities [2] by targeting on several pathways such as Wnt, NF-κB, Notch, and PI3K/AKT signaling pathways [3]. Despite these biological activities of resveratrol, its low bioavailability limits its clinical applications.

Being the third most common cause of cancer mortality worldwide, colorectal cancer (CRC) causes 860,000 deaths and more than 1.85 million new cases each year [4, 5]. Risk factors for CRC include age, family history, a history of inflammatory bowel disease, and lifestyle factors such as physical activity and diet, are responsible for the onset and progression of the disease [6]. Current therapy for CRC include chemotherapy, radiotherapy, immunotherapy, bispecific antibodies, and oncolytic virus therapy [6]. These approaches are far from being satisfactory. We are in need of new strategies to tackle with this disease.

In this article, we aim to update the action of resveratrol and resveratrol analogue on colorectal cancer. We searched recent publication on PubMed with the key words “colorectal cancer” and “resveratrol” and novel approaches, including nanoencapsulation, combination therapy, hybrid molecule, bioinformatics and systems biology, targeting of new pathways by resveratrol on CRC were discovered. These novel approaches will be the focus of this article.

2. Anti-cancer activity targeting on signaling pathways

2.1 *In silico* analysis of targeting AGE-RAGE axis signaling proteins and kinases at multiple levels with calcitriol (CAL) and trans-resveratrol (RES)

In silico analysis, including molecular docking (MD), molecular dynamic simulation (MDS), MM-PBSA analysis of exploring the molecular interactions and binding affinity of resveratrol (RES) and calcitriol (CAL) with the receptor for advanced glycation end products (AGEs) (abbreviated as RAGE), showing that RES and CAL display significant binding affinity with RAGE and signaling proteins within its signaling pathway such as PI3K/AKT, ERK1/2, PKC, and NF-κB. RES and CAL can inhibit the AGE precursor methylglyoxal (MG)-induced cell proliferative activities of HCT116 colorectal cancer cells, with the IC_{50} of 110 μM and 51 nM respectively. These data suggest the possible clinical application of RES and CAL in the therapy of colorectal cancers [7].

2.2 The therapeutic effect of resveratrol on colorectal cancers through G-protein-coupled estrogen receptor

G-protein-coupled estrogen receptor (GPER), which located within the cell membrane, functions as a mediator of estrogen in the nervous, immune, cardiovascular, and reproductive systems, and participates in bone metabolism and cancer. It is known that resveratrol displays anticancer activities, however, its effects on GPER remain unanswered. Resveratrol inhibited cell viability in high GPER-expressing RKO cells, as compared to low GPER-expressing WiDr cells. Resveratrol repressed tumor growth and displayed a high survival rate in the RKO-xenografted mice model. Resveratrol also suppressed viability of organoids expressing high GPER. Further studies showed that resveratrol responded quickly to GPER and increased the protein expression of p-ERK, Bax and cleaved PARP in CRC cells [8].

2.3 Resveratrol downregulates epithelial sodium channel through activation of AMPK in human colon cancer

Epithelial sodium channels (EnaCs) participate in various steps of cancer progression, including proliferation, migration, invasion and apoptosis. Therefore, EnaCs serve as a potential target for cancer therapy. The plant anticancer phytochemical resveratrol can activate 5'-AMP-activated protein kinase (AMPK) to reduce the amount of EnaCs in the cell membrane through internalization of the beta subunit of EnaCs in kidney connecting duct cells [9]. However, the effects of resveratrol on EnaCs in colorectal cancer (CRC) remain unknown. Resveratrol activated AMPK dose-dependently. AMPK activation by resveratrol decreased the expression of EnaC beta-subunit. Treatment with resveratrol and EnaC inhibitor amiloride significantly inhibited cell viability and induced apoptosis in HCT116 and HT29 colorectal cancer cells. These data suggested that AMPK activation by resveratrol or combined treatment with resveratrol and EnaC inhibitor might be potential for cancer therapy [10].

2.4 Resveratrol increases apoptosis by orchestrating the reciprocal crosstalk between p53 and Sirt-1 in the CRC tumor microenvironment

Resveratrol suppressed cell viability, plasticity, migration, and increased apoptosis in HCT116 wild-type (WT) cells more efficiently than in HCT116 p53-deficient ($p53^{-/-}$) cells on tumor microenvironment (TME). Resveratrol induced Sirt-1 expression at concentrations lower than 5 μM, while inhibited Sirt-1 expression at concentrations higher than 10 μM on multicellular tumor microenvironment cultures. Treatment with resveratrol at high concentration significantly increased the acetylation of p53, the expression of p21, Bax, cytochrome C, caspase-3, and subsequent apoptosis in HCT116 WT cells, but not in HCT116 $p53^{-/-}$ cells. Treatment with resveratrol at high concentration increased the hyperacetylation of p53 and FOXO3a, two substrates of Sirt-1 enzyme, indicating a reciprocal crosstalk between Sirt-1 and p53 [11].

2.5 Resveratrol regulates chemosensitisation to 5-flourouracil through the β1-integrin/HIF-1α signaling pathway in CRC tumor microenvironment

The effects of β1-integrin knockdown on anticancer activities of resveratrol and 5-flourouracil (5-FU) sensitivity were studied in colorectal cancer (CRC) cell line HCT116 and 5-FU-resistant HCT116R on CRC tumor microenvironment (TME) with 3D-alginate and monolayer cultures. Resveratrol promoted CRC cell sensitivity to 5-FU by decreasing TME-induced viability, colony formation, invasion, and mesenchymal transition. Resveratrol increased the effective utilization of 5-FU to CRC cells by decreasing TME-elicited inflammation, vascularization and cancer stem cell production, while increasing apoptosis. Knockdown of β1-integrin by antisense oligonucleotides significantly eliminated these anticancer activities of resveratrol in both CRC cell lines, specifying that β1-integrin receptor is essential for the 5-FU-chemosensitising effect of resveratrol. Besides, co-immunoprecipitation analysis showed that resveratrol can interrupt the interaction between β1-integrin and HIF-1α, suggesting that resveratrol can regulate the TME-associated β1-integrin/HIF-1α signaling pathway in CRC cells [12].

3. Synthesis of novel compound based on resveratrol structure on colorectal cancer

3.1 Novel synthesized 1,3-diaryl propane-based polyphenols based on resveratrol, honokiol, and nordihydroguaiaretic acid chemical structures

To improve the anti-cancer activity, 49 derivatives of 1,3-diaryl propane-based polyphenols were designed and synthesized through claisen rearrangement reaction based on the structure feature of existing polyphenols, including resveratrol, honokiol, and nordihydroguaiaretic acid. Through two rounds of selection against a series of colorectal cancer cell lines, two lead compounds 2t and 3t were selected with the IC_{50} from 8.2±0.1 to 19.3±1.9 μM. Both compounds displayed antiproliferative activities against COLO205 cells and anti-tumor activities in COLO205 xenografted mice with the percentage of tumor growth inhibition (TGI values) from 38% to 58%, warranting further studies for their therapeutic application [13].

3.2 Chemopreventive activities of a synthetic resveratrol-curcumin hybrid derivative

A hybrid molecule of resveratrol and curcumin, PQM-162 ((*E*)-3-(4-hydroxy-3-methoxyphenyl)-*N*'-((*E*)-4-methoxybenzylidene) acrylohydrazide), was synthesized by molecular hybridization using a hydrazone functionality as a spacer moiety between pharmacophoric fragments motivated by parent compounds. The chemopreventive activities of PQM-162 were assessed against pre-neoplastic lesions elicited in the colon

of Swiss mice and evaluated by three modes: simultaneous treatment, pretreatment, and post-treatment. PQM-162 decreased the formation of aberrant crypt foci in simultaneous treatment and post-treatment. PQM-162 reduced the expression of *TNF*-α and *COX-2* genes, while increased the expression of *Nrf2* gene. PQM-162 also decreased the protein expression of COX-2, PCNA, and β-catenin, while up-regulated Nrf2 protein expression. These data suggest a therapeutic activities of PQM-162 on colon pre-neoplastic lesions intervening in the cell proliferation, antioxidant, and anti-inflammatory pathways [14].

4. Nano encapsulation to improve resveratrol activities

4.1 Res@ZIF-8/TA Nanoparticles

Resveratrol is a polyphenolic compound that can inhibit various cancers, including breast cancer, colon cancer, gastric cancer, liver cancer, and leukemia. However, the low water solubility and quick clearance *in vivo* restrain its clinical application. Fabrication of resveratrol into nanoparticles (NPs) will be a feasible way to overcome these weaknesses. Therefore, resveratrol was packed into nanoparticles by using zeolitic imidazolate (ZIFs), together with tannic acid under mild reaction condition to become Res@ZIF-8/TA NPs. Addition of tannic acid to ZIFs fortifies these nanoparticles with good biocompatibility. The resulting Res@ZIF-8/TA NPs can respond to acid environments and release resveratrol in a controlled manner. Cell-based experiments showed that Res@ZIF-8/TA NPs can inhibit cell migration and invasion, and promote cell apoptosis in MC38 mouse colon cancer cells. These studies suggested good bioavailability and biocompatibility of Res@ZIF-8/TA NPs for cancer therapy [15].

4.2 Encapsulation of phytoalexin isorhapontigenin in cyclodextrins increases its stabilization and anti-proliferative activity to colorectal cancer

Isorhapontigenin (trans-3,4',5-trihydroxy-3'-methoxystilbene), a resveratrol analogue of the stilbenoid family, harbors a variety of biological activities, including antimicrobial, anti-inflammatory, antioxidant, antidiabetic, cardioprotective, and anticancer activities [16]. Isorhapontigenin grasps the attention of researchers in the last decade due to its better bioavailability than resveratrol[16]. Isorhapontigenin displayed similar cytotoxicity to Caco-2 colorectal cancer cells to that of piceatannol and resveratrol. Encapsulation of isorhapontigenin in 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) doubles its water solubility than other hydroxylated stilbenes and the complex was much stable at a pH below 9 and refrigeration temperatures, and retain more than 78% of isorhapontigenin after storage of 12 weeks, compared with 15% of free form. These studies suggest that isorhapontigenin/HP-β-CD complex would be an

ideal formulation for further therapeutic intervention [16].

4.3 Improvement of the physicochemical properties of rhapontigenin, a cytotoxic resveratrol analogue, for colon cancer

The methoxylated stilbene rhapontigenin is a better candidate for oral administration than hydroxylated stilbene resveratrol due to its better bioavailability. However, they display lower hydrophilicity that restrains their usage. Therefore, encapsulation in cyclodextrins is used to improve the physicochemical properties of rhapontigenin. The encapsulated rhapontigenin, especially in hydroxypropyl-β-CD (HP-β-CD), displayed much better water solubility, stability, and storage. These data indicate that encapsulation can improve the physicochemical properties of bioactive compounds for higher solubility and lower degradation [17].

5. Metabolism and metabolite analysis

5.1 Application of the rapid high performance liquid chromatography with photodiode array detection (HPLC-PDA) method to analyze the effect of resveratrol on metabolism and cellular uptake of erlotinib

Erlotinib, a selective epidermal growth factor receptor inhibitor, is used for the therapy of non-small cell lung cancer and pancreatic cancer. Cytochrome P450 3A (CYP3A) is involved in the metabolism of the drug. The phytochemical resveratrol is known to inhibit CYP3A enzyme and may function as an inhibitor for the metabolism of erlotinib. A rapid high performance liquid chromatography with photodiode array detection (HPLC-PDA) method was employed for the quantification of erlotinib in liver microsomes and cancer cells and assay for the activity of resveratrol on metabolism and cellular uptake of erlotinib. Resveratrol acted as a strong inhibitor of erlotinib metabolism *in vitro* with the IC_{50} of 4.03 μM. However resveratrol displayed no effect on cellular uptake of erlotinib after 1 h of incubation in human colorectal cancer HT-29 cells [18].

5.2 In vivo metabolite profiling of DMU-212, a resveratrol analogue, in $Apc^{Min/+}$ mice using UHPLC-Q/Orbitrap/LTQ MS

The *in vivo* metabolite profiling of 3,4,5,4'-trans-tetramethoxystilbene (DMU-212), a resveratrol analogue with stronger antiproliferative activity and more bioavailability, was established by ultra-high performance liquid chromatography-quadrupole/orbitrap/linear ion trap mass spectrometry (UHPLC-Q/Orbitrap/LTQ MS) in the AcquireX™ intelligent data acquisition mode, combining the exact mass and structural information in the colorectal adenoma (CRA) spontaneous model $Apc^{Min/+}$ mice after oral dosage of 240 mg/kg for 3 weeks. A total of 63 metabolites of DMU-212 were obtained, including 48, 48, 34 and 28 metabolites in intestinal contents, liver,

serum, and colorectal tissues of the Apc$^{Min/+}$ mice. The metabolic pathways involved in the metabolism were found to include demethylation, oxidation, desaturation, methylation, acetylation, glucuronide and cysteine conjugation. Molecular docking analysis of the key metabolites with the microbial bile salt hydrolases (BSHs), the enzymes involved in the pathogenesis of colon cancer via the bile acid signaling pathway, showed the strong binding affinity of some DMU-212 metabolites to BSHs. Further analysis of the active constituents of DMU-212, their action mechanisms, and application for CRA prevention are urging [19].

6. Combination therapy

6.1 Combination therapy of peanut skin procyanidins and resveratrol to colorectal cancer

Combination therapy is a way to increase the anti-cancer activities by combination of two or more drugs, while reducing their side effects at the same time [20, 21]. The combined anti-cancer effects of procyanidins (isolated from peanut skin) and resveratrol (isolated from peanut buds) were evaluated in CACO-2 and HCT-8 colorectal cancer cells, and HEPG-2 and HUH-7 hepatoma cells. Both procyanidins and resveratrol can inhibit cell proliferation of all tested cells in a concentration-dependent manner, whereas synergistic effects were only observed in CACO-2 cells. Drug combination inhibited colony formation, promoted apoptosis, arrested cell cycle progression at G_0/G_1 stage, inhibited the phosphorylation of Th308, Ser473 of AKT, ERK, and promoted the phosphorylation of IKBα and NF-κB in CACO-2 cells, indicating that the synergistic effects were through the AKT, ERK, and NF-κB signaling pathways. Combination therapy of procyanidins and resveratrol for anti-cancer activities are emerging [22].

7. Bioinformatics and system biology analyses of resveratrol

7.1 Detection of resveratrol as a potential drug for both COVID-19 and colorectal cancer by bioinformatics and system biology techniques

Bioinformatics and system biology techniques were employed to detect the intrinsic link between COVID-19 and colorectal cancer. By using RNA sequencing datasets, 161 common differentially expressed genes (DEGs) were selected to identify hub genes and key modules. The datasets showed that transcription factors-gene interactions, co-regulatory networks with DEGs-miRNAs of common DEGs, and possible therapeutic drugs were predicted. Resveratrol, as one of the ten isolated potential drugs, showed promising for the therapy of these two diseases [23].

7.2 Targeting 17-beta-hydroxysteroid dehydrogenase (17-beta-HSD1)

with natural products for treatment of colorectal cancer

To look for natural plant metabolites that target on 7-beta-HSD1, an enzyme that involved in steroid metabolism in the development and proliferation of colorectal cancers, computational prediction by Avogadro, ADMET lab 2.0, SWISS-MODEL, AutoDock, and Gromacs was used to predict factors including the regulation of cancer-related proteins, epigenetic factors and reactive oxygenase species. Five lead molecules were chosen from a pool of plant metabolites based on their affinity for the 17-beta-HSD1 enzyme. The top two compounds with highest binding affinity are resveratrol (DG 11.29 kcal/mol) and folate (DG 12.23 kcal/mol) with low Ki values, which compounds display a stable conformation with 17-beta-HSD1 by molecular dynamic simulation. These compounds may provide an opportunity for future colorectal cancer therapy by targeting on 17-beta-HSD1 enzyme [24].

8. Conclusive remarks and perspective direction

A great variety of health beneficial effects of resveratrol is known to come from its targeting on multiple signaling pathways, including the Wnt, Notch, PI3K/AKT and NF-κB pathways [3]. Evidences in this article show that resveratrol also targets on other signaling pathways for its anti-colorectal cancer activity, and probably these effects can be expanded to the therapy of other diseases by intervening the same pathways. One of its target is G-protein-coupled estrogen receptor (GPER). Resveratrol can inhibit cell viability in high GPER-expression RKO cells, viability of organoids with high GPER expression, and tumor growth of RKO-xenografted mice. Resveratrol also increased the survival rate of RKO-xenografted mice [8]. Another cellular target of resveratrol is epithelial sodium channels (EnaCs). Resveratrol can activate 5'-AMP-activated protein kinase (AMPK), and in turn to downregulate EnaCs on the cell membrane. Combined treatment of resveratrol with EnaC inhibitor amiloride substantially suppressed cell viability and elicited apoptosis in HCT116 and HT29 colorectal cancer cells [10]. Resveratrol targets on receptor for advanced glycation end products (RAGE) by binding to RAGE and downstream signaling proteins including PI3K/AKT, ERK1/2, PKC, and NF-κB, and thus can inhibit the AGE precursor methylglyoxal (MG)-induced cell proliferation of HCT116 colorectal cancer cells [7]. Resveratrol can regulate the crosstalk between Sirt-1 and p53, and thus decreased cell viability, plasticity, migration, and induced apoptosis in HCT116 wild-type (WT) cells more than in HCT116 p53-deficient ($p53^{-/-}$) cells on TME [11]. Resveratrol also targets and modulates the TME-associated β1-integrin/HIF-1α signaling pathway in CRC cells [12].

High-throughput screening (HTS) has speeded up the discovery and development of small molecule drugs for clinical application [25]. Modification of current drugs of

known activity and action mechanism for development of new drug proves to be a feasible way to look for new drugs [26]. PQM-162 ((*E*)-3-(4-hydroxy-3-methoxyphenyl)-*N*'-((*E*)-4-methoxybenzylidene) acrylohydrazide), a hybrid molecule of resveratrol and curcumin synthesized by molecular hybridization, displayed therapeutic activities on colon pre-neoplastic lesions of Swiss mice by intervening in the cell proliferation, antioxidant, and anti-inflammatory pathways [14]. Another strategy is to synthesize a couple of 1,3-diaryl propane-based polyphenols based on the structure feature of existing polyphenols, including resveratrol, honokiol, and nordihydroguaiaretic acid. Two lead compounds 2t and 3t were selected and displayed antiproliferative activities against COLO205 cells and anti-tumor activities in COLO205 xenografted mice with TGI values from 38% to 58% [13]. These studies suggest the potential development of novel drugs from the existing bank of many available drug compounds.

Resveratrol possesses many biological activities, including anti-cancer activity. However, the low bioavailability and solubility compromise its biological activity [1, 27]. Package into nanoparticles is a good way to solve these drawbacks caused by conventional drug, such as low solubility, instability, and rapid clearance [27]. Nanoencapsulation of resveratrol for lung cancer treatment has been proposed [27]. Here we provide three examples of packing resveratrol as nanoparticles for anti-colorectal cancer activity, including one case packed in zeolitic imidazolate with tannic acid (Res@ZIF=8/TA nanoparticles) [15], and two in 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) [16, 17]. These nanoparticles yielded better solubility, stability, and storage and proved their anticancer activities in colorectal cancer cells and xenografted model mice.

Looking into the future, combined tools of bioinformatics, system biology, and computational prediction can be used to link datasets such as RNA sequencing, metabolomics, proteomics, and look for potential drugs or drug target in various diseases. Modification of current drugs can create novel molecule for better therapeutic application. Combination of several drugs into a single formula is workable to increase drug activity with less side effects. The use of nanotechnology for packing drugs can improve drug physiochemical properties such as bioavailability, stability, solubility, slow or controllable release. These improvements can help in clinical application of resveratrol in the future.

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Table I: Anti-colorectal cancer activity of resveratrol on signaling pathways

Resveratrol/Other compound	Method/Analysis	Cells	Target(s)/Activities	Reference
Resveratrol and calcitriol	**1.** *In silico* analysis, including molecular docking (MD), molecular dynamic simulation (MDS), MM-PBSA analysis of exploring the molecular interactions and binding affinity of resveratrol (RES) and calcitriol (CAL) with the receptor for advanced glycation end products (AGEs) **2.** Cell proliferation assay of HCT116 colorectal cancer cells	HCT116	**1.** Targets: AGE-RAGE axis signaling proteins and kinases at multiple levels **2.** Activity: (1) RES and CAL show high binding affinity with RAGE and signaling proteins; (2) Both compounds decreased methylglyoxal-induced cell proliferation of HCT116 cells	7
Resveratrol	**1.** Cell viability assay **2.** Tumor growth and survival rate of RKO-xenografted mice **3.** Cell viability assay of organoids expressing high GPER	RKO, WiDr	**1.** Target: G-protein-coupled estrogen receptor (GPER) **2.** Activities: (1) Resveratrol decreased cell viability of RKO cells; (2) Resveratrol decreased tumor growth and increased survival rate of RKO-xenografted mice; (3) Resveratrol decreased viability of high-GPER expressing organoids	8
Resveratrol	**1.** Cell viability **2.** Apoptosis **3.** Western blotting	HCT116, HT29	**1.** Target: Epithelial sodium channel (EnaCs) **2.** Activities: (1) Treatment with resveratrol and EnaC inhibitor amiloride decreased cell viability and activated apoptosis in both cells. (2) AMPK activation by resveratrol decreased expression of EnaC beta-subunit.	10
Resveratrol	**1.** Cell proliferation **2.** Western blotting **3.** Immunostaining **4.** Plasticity assay **5.** Wound healing assay **6.** Multicellular tumor microenvironment (TME)	HCT116, HCT116 $p53^{-/-}$ cells	**1.** Targets: p53 and Sirt-1 signaling pathways (reciprocal crosstalk of p53 with Sirt-1) **2.** Activities (all in TME): (1) Resveratrol inhibited cell viability, plasticity, migration, and increased apoptosis more in HCT116 WT cells; (2) Resveratrol at high concentration increased p53 acetylation, p21, Bax, cytochrome C, caspcase-3; apoptosis in HCT116 WT cells; (3) Resveratrol at high concentration increased p53 hyperacetylation and FOXO3a in HCT116 WT cells	11

Resveratrol and 5-flourouracil (5-FU)	**1.** Cell viability **2.** Colony formation **3.** Invasion **4.** Epithelial mesenchymal transition **5.** Inflammation **6.** Vascularization **7.** Cancer stem cell production **8.** Knockdown of β1-intergin **9.** TME	HCT116, 5-FU-resistant HCT116 R cells	**1.** Target: the TME-associated β1-integrin/HIF-1α signaling pathway; **2.** Activities: (1) Resveratrol increased CRC cell sensitivity to 5-FU by decreasing TME-induced viability, colony formation, invasion, and mesenchymal transition. (2) Resveratrol increased the effective utilization of 5-FU to CRC cells by decreasing TME-elicited inflammation, vascularization and cancer stem cell production, while increasing apoptosis. (3) Knockdown of β1-integrin by antisense oligonucleotides eliminated these anticancer activities of resveratrol in both CRC cells	12

Table II: Novel synthesized compounds on colorectal cancer

Novel synthesized compounds	Method/Analysis	Cells/Tissues	Effects/Activities	Reference
1,3-diaryl propane-based polyphenols	These compounds were designed and synthesized through claisen rearrangement reaction based on the structure of existing polyphenols, including resveratrol, honokiol, and nordihydroguaiaretic acid.	COLO205	**1.** Two lead compounds 2t and 3t were selected against colorectal cancer cells with the IC_{50} from 8.2±0.1 to 19.3±1.9 μM. **2.** Both compounds displayed antiproliferative activities against COLO205 cells and anti-tumor activities in COLO205 xenografted mice with TGI values from 38% to 58%.	13
Resveratrol-curcumin hybrid derivative (PQM-162)	This molecule was synthesized by molecular hybridization using a hydrazone functionality as a spacer moiety between pharmacophoric fragments motivated by parent compounds.	Pre-neoplastic lesions in the colon of Swiss mice	**1.** PQM-162 decreased the formation of aberrant crypt foci in simultaneous treatment and post-treatment. **2.** PQM-162 reduced the expression of *TNF*-α and *COX-2* genes, while increased the expression of *Nrf2* gene. **3.** PQM-162 also decreased the protein expression of COX-2, PCNA, and β-catenin, while up-regulated Nrf2 protein expression.	14

Table III: Nanoencapsulation of resveratrol and resveratrol analogue to improve the physicochemical properties

Nanoparticles	Method/Analysis	Cells	Effects or improved properties	Reference
Res@ZIF-8/TA NPs (with good biocompatibility)	Resveratrol was packed into nanoparticles by using zeolitic imidazolate (ZIFs), together with tannic acid under mild reaction condition to become Res@ZIF-8/TA NPs.	MC38 mouse colon cancer cells	**1.** Decrease in Cell migration **2.** Decrease in Cell invasion **3.** Increase in Apoptosis	15
Isorhapontigenin/HP-β-CD complex	Conjugation of isorhapontigenin into 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) to have isorhapontigenin/ HP-β-CD complex	CACO-2	**1.** Encapsulation doubles the water solubility of isorhapontigenin than other hydroxylated stilbenes **2.** The complex was much stable at a pH below 9 and refrigeration temperatures **3.** The complex retain more than 78% of isorhapontigenin after storage of 12 weeks, compared with 15% of free form.	16
Rhapontigenin/HP-β-CD complex	Conjugation of rhapontigenin into 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) to make rhapontigenin/ HP-β-CD complex		The encapsulated rhapontigenin/HP-β-CD complex displayed much better water solubility, stability, and storage.	17

Table IV: Resveratrol on drug metabolism and *in vivo* metabolite profiling analyses of resveratrol analogue

Resveratrol/ Target drug	Method/Analysis	Cells	Effects	Reference
Resveratrol/ Erlotinib	**1.** A rapid high performance liquid chromatography with photodiode array detection (HPLC-PDA) method **2.** The quantification of erlotinib in liver microsomes and cancer cells and assay for the activity of resveratrol on metabolism and cellular uptake of erlotinib	HT-29	**1.** Resveratrol strongly inhibited erlotinib metabolism *in vitro* with the IC_{50} of 4.03 μM; **2.** Resveratrol had no effect on cellular uptake of erlotinib after 1 hour of incubation in HT-29 cells	18
Resveratrol analogue	Method/Analysis	Tissues	In vivo profile	Reference
3,4,5,4'-trans-tetramethoxystilbene (DMU-212)	An ultra-high performance liquid chromatography-quadrupole/orbitrap/linear ion trap mass spectrometry	Colorectal adenoma	**1.** A total of 63 metabolites of DMU-212 were obtained, including 48, 48, 34 and 28	19

	(UHPLC-Q/Orbitrap/LTQ MS) in the AcquireX™ intelligent data acquisition mode, combining the exact mass and structural information in the colorectal adenoma (CRA) spontaneous model Apc$^{Min/+}$ mice after oral dosage of 240 mg/kg for 3 weeks		metabolites in intestinal contents, liver, serum, and colorectal tissues of the Apc$^{Min/+}$ mice. **2.** The involved metabolic pathways include demethylation, oxidation, desaturation, methylation, acetylation, glucuronide and cysteine conjugation. **3.** Molecular docking analysis showed the strong binding affinity of some DMU-212 metabolites to the microbial bile salt hydrolases (BSHs).	

Table V: Combination therapy

Combined drugs	Method/Analysis	Cells	Effects	Reference
Resveratrol and procyanidins	**1.** Cell proliferation **2.** Colony formation **3.** Apoptosis **4.** Cell cycle **5.** Western blotting	CACO-2	**1.** Decrease in cell proliferation **2.** Decrease in colony formation **3.** Increase in apoptosis **4.** Arrest of cell cycle at G_0/G_1 stage **5.** Decrease in phosphorylation of Thr308, Ser473 of AKT, ERK **6.** Increase in phosphorylation of IKBα and NFκB	22

Table VI: Using bioinformatics, system biology, and computational prediction to look for potential drugs and potential targets

Potential drug(s)	Method/Analysis	Target(s)	Reference
One of ten isolated drugs is resveratrol	Bioinformatics and system biology **1.** RNA sequencing datasets **2.** Differentially expressed genes	Linked targets: COVID-19 and colorectal cancer	23
Two compounds with highest binding to 17-beta-HSD1 are: resveratrol and folate	**1.** Computational prediction by Avogadro, ADMET lab 2.0, SWISS-MODEL, AutoDock, and Gromacs **2.** Molecular dynamic simulation	17-beta-hydroxysteroid dehydrogenase (17-beta-HSD1)	24