Received: 03 January 2023 | Revised: 13 February 2023 | Accepted: 26 February 2023
DOI: 10.22034/ecc.2023.379480.1586
Journal of Medicinal and Pharmaceutical Chemistry Research
SAMI

FULL PAPER

Resveratrol in cancer chemotherapy: Is it a preventer, protector, or fighter?

Seema Mahmood Kasim[a] |Noora Thamer Abdulaziz[b] |Mahmood Hashim Jasim[a] |Yasser Fakri Mustafa[a,*]

[a]*Pharmaceutical Chemistry Department, College of Pharmacy, University of Mosul, Mosul, Iraq*

[b]*Department of Pharmaceutics, College of Pharmacy, University of Mosul, Mosul, Iraq*

Cancer is a virulent disease that is regarded as a black-hearted and evil-minded illness in many human civilizations because it develops silently and without warning until it reaches a life-threatening stage. In the management of cancer, chemotherapy represents the principal option but has significant toxic effects that negatively influence the patient's physiology and psychology. To improve the chemotherapy efficacy, scientists proposed several adjuvant approaches, including the use of fighters with an additive effect that reduces the chemotherapeutic agent dose, and thus the occurrence of toxic effects, protectors to preserve normal tissues, and preventers by inducing apoptosis in cancerous cells as they develop. It seems that nature can provide these adjuvant agents with high quality. Resveratrol is one of the most studied natural agents due to its promising effects in cancer treatment. This review aimed to highlight these effects based on exploring the most recent information concerning this natural polyhydroxy product. The authors concluded that resveratrol can act as a potential chemotherapy alleviator by inhibiting carcinogenesis and many of its initiating enzymes and proteins, modulating many chemotherapy-related toxic effects, and potentiating the toxic effects inside cancerous cells via multiple pathways.

***Corresponding Author:**
Yasser Fakri Mustafa
Email:Dr.yassermustafa@uomosul.edu.iq
Tel.: +009647701615865

KEYWORDS

Resveratrol; chemopreventer; chemoprotector; chemofighter; cancer; chemotherapy.

Introduction

Malignant tumors, another name for cancerous diseases, are a serious public health concern that not only causes patients to suffer excruciating pain, but also place a significant financial burden on their families and society [1-8]. Cancer has overtaken many other diseases in terms of total mortality and is now the leading cause of death for people worldwide [9-16]. According to statistics, there were approximately 90.5 million cancer patients in 2015, and nearly 14.1 million new cases-aside from melanoma-occurred annually [17]. Despite enormous efforts to ameliorate the condition and develop novel remedies, such as immunotherapy and microscopic surgery, chemotherapy remains the primary concept used in clinics. However, chemotherapy frequently causes many toxic-related effects and results in unpleasant and irritating events [18-26].

Naturally-developed products have long been regarded as one of the most vital and essential data sources in drug development and discovery. For centuries, humans have depended on these products and/or herbal compositions for maintaining health,

preventing illness, and improving mental and physical health status [27-35]. Many research findings have shown that some naturally-developed products, when combined with chemotherapeutic agents, can act as chemoprotectors, chemopreventers, or chemofighters, affording a reduction in chemotherapy-related toxic effects and improving clinical outcome [36].

Resveratrol (RVL), which its chemical backbone is displayed in Figure 1, is a naturally-developed polyhydroxylated stilbenoid that is most commonly found as a white powder with reasonable aqueous (0.03 mg/mL) solubility. The structural formula of RVL is made up of one phenolic ring and one resorcinolic ring linked by a double bond, which allows for configurational isoforms of the *cis* and *trans* phenotypes. In comparison, the latter isoform is more prevalent in dietary products than the former, as reported in Table 1, and also has the best bioactive properties [37].

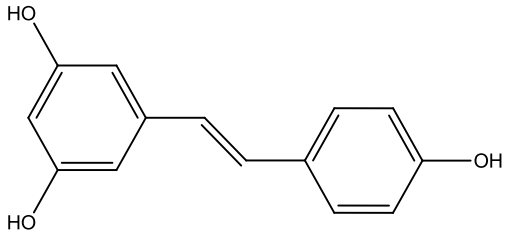

FIGURE 1 Chemical backbone of RVL.

TABLE 1 The calculated amount of RVL (w/w) in various dietary products

Dietary product	Calculated amount (µg/g)
Grape skin (fresh)	50-100
Itadori leaf (aged)	370-379
Itadori leaf (new)	867- 884
Itadori root (raw)	2170-2180
Itadori stem (aged)	83-86
Itadori stem (new)	497-503
Itadori tea (dry)	974-976
Peanut buffer	0.16-0.50
Peanuts (boiled)	1.80-7.10
Peanuts (fresh)	0.07-1.8
Red wine	980-1800 (µg/L)

A vast spectrum of bioactivities, such as antioxidant, antiviral, anti-inflammatory, antifungal, anticancer, and anti-aging effects, have been linked to RVL. The vast majority of these bioactivities can be attributed to the RVL's intriguing multi-phenolic hydroxyl groups. This structural feature can permit RVL to neutralize harmful free radicals and produce more stable quenched molecules with lower cytotoxicity than damaging radicals [38-41].

Several studies demonstrated that RVL might prevent three cellular processes-tumor initiation, tumor promotion, and tumor progression-that lead to the cancer development. This information attracted attention and prompted further research into RVL. According to recent research, RVL has cytoprotective properties that can shield many organs, including the heart, liver, and brain, from harmful effects of chemotherapy. RVL and chemotherapeutics can be administered together to treat cancer while reducing side effects and improving therapeutic efficacy. Recent studies have described the therapeutic benefits and cytoprotective properties of RVL in various medical conditions, including those connected to autoimmune and neoplastic diseases [42].

As far as we are aware, there has not been a review article that specifically discusses RVL as a remedy for reducing associated toxic effects and boosting therapeutic efficacy in cancer chemotherapy. This study sought to clarify the RVL function in cancer chemotherapy and determine whether it serves as a preventer, protector, or fighter. The mechanisms, potential drawbacks, and potential clinical applications of the RVL-alleviative therapy are further discussed.

RVL as a protector in cancer chemotherapy

The negative impacts of chemotherapeutic agents represent a barrier to their widespread use in cancer treatment. RVL, a

versatile, naturally evolved molecule, demonstrated shielding properties capable of mitigating the negative effects of cancer chemotherapy.

RVL as a cardioprotector in cancer chemotherapy

Cardiotoxicity is a frequent related-toxic effect brought on by chemotherapy drugs. Congestive heart failure, arrhythmias, myocarditis, and dilated cardiomyopathy are typically caused by clinically used anthracycline antibiotics like doxorubicin and daunorubicin. Damaging free radical-induced oxidative stress is a well-known contributor to cardiovascular toxic events. In this regard, doxorubicin was discovered to boost the generation of these unpaired molecules in myocardial cells [43].

The protecting properties of four naturally-developed antioxidants involving RVL were examined by Sheu and his colleagues. This research team discovered that when these antioxidants were individually combined with doxorubicin in cancer treatment, the intracellular levels of damaging free radicals were dramatically reduced. Furthermore, the superoxide dismutase levels responsible for the removal of these unpaired molecules were raised. The RVL antioxidant capacity was discovered to be superior at neutralizing damaging free radicals among those tested. To lessen the cardiotoxicity of doxorubicin-based cancer chemotherapy, RVL can be used as an effective complement [44].

Further research revealed that cardiotoxic effects of these natural alkaloidal antibiotics may be due to two-electron reduced anthracycline antibiotic metabolites, such as the more cardiotoxic doxorubicinol derived from the parent drug doxorubicin. This metabolically reduced metabolite's high cardiotoxicity can be credited to its propensity to interact with calcium, magnesium, and sodium-mediated ATPases. Disruption of the calcium ion that connects electric stimulation and cell contraction may be responsible for doxorubicinol cardiotoxicity [45]. In particular, cytosolic enzymes called carbonyl reductases and aldo-keto reductases mediate the enzymatic degradation of anthracycline antibiotics. Therefore, it is thought that the inhibitors of these reductases scaled back the cadiotoxic effects of these antibiotics [46]. According to Ito and his group, doxorubicin's cardiotoxicity was decreased by the RVL ability and its analog to suppress carbonyl reductase 1. This analog had methoxy and amino groups at positions 5 and 4', respectively [47].

In addition to organic chemotherapeutic drugs, there is an inorganic agent named arsenic trioxide (As_2O_3) that is mainly applied for managing blood-related and solid tumors. This agent, however, is not without toxicity because it causes multiple toxicities to the heart, liver, and kidney; such toxicity may result in sudden death. Similar to anthracycline antibiotics, the underlying mechanism of As_2O_3's toxicity is related to oxidative overload, which hits cellular macromolecules, resulting in their malfunction [48]. According to Zhao *et al.*, pretreatment with RVL (3 mg/kg) one hour in advance of the As_2O_3 regime can protect the patient from the cardiotoxicity caused by As_2O_3 and reduce myocardial ischemia, genomic instability, and lipid peroxidation [49].

RVL as a nephroprotector in cancer chemotherapy

Regarding the inorganic chemotherapeutic agent As_2O_3, it is known that chronic arsenic exposure can lead to degenerative changes in kidneys and that eating foods and drinking water contaminated with arsenic can damage kidneys. Furthermore, As_2O_3 treatment of leukemia and myeloma has been linked to nephrotoxicity, as evidenced by elevated

blood urea, creatinine, and protein thresholds in clinical studies [50]. In 2013, Yu and his research group discovered that RVL could speed up the second metabolic phase of arsenic and consequently its excretion, drastically reducing arsenic deposition, tubular malformations, and As_2O_3-based nephrotoxicity [51].

RVL as a hepatoprotector in cancer chemotherapy

Hepatic tissues are important for the detoxification of both endogenous and exogenous chemicals, but they can be further harmed by these harmful chemicals. As_2O_3 has also been linked to hepatotoxicity, which is linked to the production of harmful free radicals, in addition to cardiotoxicity and nephrotoxicity. According to Zhang *et al.*, RVL could reduce the hepatic arsenic deposition and boost the antioxidant capacity of the associated antioxidant enzymes, thereby reducing As_2O_3-based hepatotoxicity [52]. Further research demonstrated that RVL's potent antioxidant activity could shield the liver from acetaminophen and pyrogallol-based hepatotoxicity [53].

RVL as a GIT-protector in cancer chemotherapy

The GIT tissues are further susceptible to the toxicity associated with cancer chemotherapy that manifests as nausea, vomiting, anorexia, constipation, and/or diarrhea. Acetylsalicylic acid, a non-selective NASID prototype, is frequently employed to attenuate the signs and symptoms of inflammation, fever, and pain. This NSAID is recommended for participation in cancer prevention, especially to lower the risk of colorectal neoplasms, according to a recent study [54].

The primary adverse effect of acetylsalicylic acid-based therapy, however, is gastric tissue ulceration, which is related to the downregulation of the barrier protection COX-1 enzyme. According to Dey *et al.*, a low dose of RVL (2 mg/kg) can safeguard the gastric mucous membrane from NSAID-induced GIT toxicity, whereas a high dose of RVL (10 mg/kg) showed an adverse effect that may have been caused by disturbance in harmony between endothelial nitric oxide synthase and COX-1 [55]. Zhu *et al.* created the RVL-acetylsalicylic acid mutual prodrug, acting as an entity with the capability of releasing acetylsalicylic acid and RVL simultaneously to further mitigate the adverse effects brought on by acetylsalicylic acid-based therapy. While the majority of this mutual prodrug was shuttled out of the stomach, some of its components were detected intact in colonic tissues removed between one and two hours after administration [56].

One more study carried out by Ko *et al.* demonstrated that pretreatment of male Wistar rats with whole grape juice containing high levels of RVL could improve glomerular filtration, renal tubular cell vacuolization, and gastric emptying rate, thereby reducing the risk of cisplatin-caused GIT abnormalities [57].

RVL as a dermoprotector in cancer chemotherapy

Dermal tissues play numerous important roles in protecting the body from harmful environmental agents and providing immunological surveillance against infectious agents. The ultraviolet irradiation (UVI) has the ability to cause apoptosis, suggesting some medical applications. But in addition to genetic and environmental factors, exposure to UVI is further considered one of the foremost factors responsible for skin cancer (65–90%) [58].

Numerous studies have suggested that RVL can prevent UVI-induced skin cancer by regulating the proteases involved in apoptosis. In SKH-1 hairless mice, topical application of RVL significantly reduced UVI-promoted peroxide production, leukocyte

infiltration, and UVI-caused skin edema, according to Afaq and his colleagues' 2003 research. Long-term topical application of RVL, either pre- or post-treatment, has been reported to be able to reduce the incidence of tumors and postpone the start of photocarcinogenesis [59]. On the other hand, the short-term topical application of RVL can reduce cellular proliferation and phosphorylation of surviving cells. Only a few studies revealed that certain cell cycle ordering systems, including apoptotic-suppressing proteins and cell signal transduction pathways, are involved in RVL-promoted chemoprotection. This RVL potential results in minimizing the incidence of UVI-based photocarcinogenesis [60].

RVL as a preventer in cancer chemotherapy

In many studies, RVL has been shown to prevent carcinogenesis by reducing the effects of factor-induced carcinogenesis in addition to act as a protector all through cancer chemotherapy. For example, Revel *et al.* discovered that RVL (50 mg/kg/week) could protect pulmonary tissues from the carcinogenic potential of teratogen benzo[α] pyrene [61]. Tessitore *et al.* found that taking RVL (200 mg/kg/day) orally reduced the amount of cancerous cells in an azoxymethane-induced colon carcinogenesis in a rat model [62]. RVL pre-treatment could partly avert tetrachloromethane-induced hepatic tumors, according to research by Fan and his colleagues [63]. Furthermore, while daily consumption of RVL had no effect on tumor mass in a rat model of carcinogenesis caused by 7,12-dimethyltetraphene, it caused significant reductions in tumor occurrence and multitude, extending the time before malignant transformation [64].

RVL as a fighter in cancer chemotherapy

Many body processes included in vital systems that regulate the cell cycle, apoptosis, and inflammation could be affected by RVL. In addition to its roles in cancer chemotherapy as a protector and preventer, RVL also demonstrates promising anti-cancerous activity [65]. It is now common knowledge that a single treatment frequently exhibits ineffectiveness, partial efficacy, and treatment failure. Newly invented mutual therapies, which involve coupling multiple active agents at once, frequently produce superior curative results [66].

In a breast cancer and other estrogen-promoted tumors, the presence of high estrogen level can be regarded as a trigger factor for carcinogenesis due to the generation of the adduct between this natural hormone and DNA [67]. It was documented that this adduct formation is effectively suppressed by RVL. Wu *et al.* discovered that, by causing S-phase arrest, RVL can increase the *in vitro* cytotoxic potential of the known antitumor drug, 5-fluorouracil, on the model of mouse hepatocellular carcinoma cells. Similarly, studies by Dun *et al.* showed that RVL could boost the same drug's cytotoxic potential through such a mechanism both *in vitro* and *in vivo* [68].

The cancer-fighting impact of RVL was also investigated against human HL-60 leukemia cells, both as a single agent and in combination with roscovitine [69]. Following a combined treatment for 24 hours and a subsequent 48-hour post-incubation with the RVL involvement, a startling coalescence was shown. With the RVL addition, the population of cancerous cells was reduced by around 80% at multiple smaller concentrations of roscovitine [70].

Another *in vitro* study looked at the cancer-fighting activity of RVL in combination with the anticancer alkylating drug, melphalan, for the treatment of breast carcinoma. According to the findings, melphalan's antitumor effects in the MCF-7 and MDA-MB-231 cell lines derived from breast cancer may be enhanced by RVL. It is interesting to note that sequenced

intervention with RVL and melphalan produced more cytotoxic effects associated with chemotherapy than did sequenced intervention with melphalan and RVL. This finding might be explained by RVL's capacity to make the test cancer cells more susceptible to the cell-killing effects of melphalan [71]. Similarly, it has been disclosed that RVL could make multiple myeloma and Hodgkin's non-lymphoma cell lines more susceptible to pegylated cell death, increasing paclitaxel's antineoplastic effectiveness [72].

The down-regulation of the mTORC1 mechanism, which is potently suppressed by rapamycin and its derivatives, can halt the growth of tumor cells in various malignant tumor models. The antitumor activity of rapamycin in lines belonging to breast cancer was observed to be enhanced when combined with RVL, and it was found that RVL greatly reduced the rapamycin-induced AKT phosphorylation of various nuclear proteins. This suggests that RVL could help rapamycin boost its clinical benefit [73].

A further study looked at the RVL effectiveness and clofarabine acting together to treat mesothelioma MSTO-211H cells, a malignancy model. The coupling index was calculated, and it was discovered that this mix of treatments could have a potent synergistic antineoplastic influence on cell models. RVL was thought to be involved in the PI3K/AKT signal transduction pathway by lowering Sp1 levels. In addition, inhibiting AKT phosphorylation and Sp1 initiation may serve as a partial mediator for the mutual antineoplastic effects of RVL and clofarabine [74].

Rationalization and future recommendations

Despite the enormous attempts undertaken to find effective treatments for cancer, it continues to rank among the leading causes of death in humans. Cancer risk is rising exponentially, and over the next 50 years, it is expected that the total number of cancer-related deaths will double. Cancer chemotherapy remains one of the most regularly utilized treatments today, but it only helps patients live longer overall at the expense of their life quality. Furthermore, chemotherapy frequently results in chemo-resistance, rapid relapse, and a slew of adverse health effects such as nephrotoxicity, cardiotoxicity, and GIT toxicity. The variety of cancers makes it difficult to identify a specific target for cancer therapy. Treatment of cancer with mutually active agents that are capable of acting on multiple targets is one of the most promising solutions to this problem.

Natural products exhibit various biological functions for the prevention, protection, and treatment of different diseases, making them one of the critical inputs in the development of new drugs. RVL is a naturally occurring polyphenol that is present in a variety of dietary components. There is a lot of research into the RVL use in the treatment and prevention of various illnesses, particularly cancer. Concerning the latter, the ability of RVL to interact with a variety of cancer-related targets at the molecular level has been investigated.

The currently available data revealed positive outcomes for considering RVL as a preventer, protector, and fighter in cancer chemotherapy, indicating that this natural product has significant potential to be involved in cancer management. These outcomes were shown both *in vitro* and *in vivo*. The low-moderate RVL doses that would quickly be enabolized to secure glucoronate and other analogs are likely to blame for the lack of side effects. It is essential to conduct some related clinical testing in addition to research using high doses of RVL in comparable experiments to confirm these encouraging findings.

There have been few spotlights concerning the potential of RVL versus individual kinds of neoplasia. The use of RVL pairing with certain other antineoplastic medications to lessen associated toxic effects and improve

clinical benefit in cancer chemotherapy has not yet been the subject of any completed or enduring clinical testing. Many research plans are centered on *in vitro* and *in vivo* veterinary investigations. It is consoling to know that researchers can gather some useful data, and then draw conclusions from these studies when planning new studies to start delivering better health outcomes.

Moreover, because RVL has a poor bioavailability, it is crucial to modify and optimize it further to develop new variants that have higher bio-availabilities and better specificities. High-throughput screening, for example, has been used to identify precise and attacking peptide ligands against various cancer cells or disease biomarkers. It is anticipated that conjugating targeting peptides to RVL against anticipated cancer cells or significant proteins of interest will significantly increase RVL's efficacy while reducing its side effects [75].

Conclusion

As a final result, it has been discovered that RVL can modulate cancer therapy by focusing on a variety of cellular and transmitter pathways involved in the tumorigenic algorithm. RVL can lessen the cancer chemotherapy-related toxic effects, including UVI-caused dermal cancer, injuries from carcinogens, cardiotoxicity, hepatotoxicity, nephrotoxicity, and GIT toxicity. In the meantime, using RVL in combination with other chemotherapeutic medications can improve the results. These encouraging findings will spur scientists to carry out more exploration of RVL's role in cancer therapy, including additional clinical testing, in-depth mechanism analyses, and the creation of new derivatives with enhanced properties. Since then, RVL is now considered a preventer, protector, and fighter (i.e. an alleviative agent) in cancer chemotherapy.

Acknowledgements

The University of Mosul/College of Pharmacy provided resources that enhanced the level of talent of this work, for which the authors are extremely grateful.

Conflict of Interest

The authors declare that there is no conflict of interest.

Orcid:

Seema Mahmood Kasim:
https://www.orcid.org/0000-0002-2061-8559
Noora Thamer Abdulaziz:
https://www.orcid.org/0000-0001-8330-7777
Mahmood Hashim Jasim:
https://www.orcid.org/0000-0002-8198-8246
Yasser Fakri Mustafa:
https://www.orcid.org/0000-0002-0926-7428

References

[1] F. Mohajer, G. Mohammadi Ziarani, A. Badiei, New advances on modulating nanomagnetic cores as the MRI-monitored drug release in cancer, *J. Appl. Organomet. Chem.*, **2021**, *1*, 143-147. [Crossref], [Google Scholar], [Publisher]
[2] N. Zarei, M.R. Rezaie, A. Jomehzadeh, Radiation hazards investigation of photon scattering by Elekta 6 MeV Linac during liver cancer treatment, *Chem. methodol.*, **2022**, *6*, 582-590. [Crossref], [Pdf], [Publisher]
[3] A. Salehi Sardoei, Review on Iranian medicinal plants with anticancer properties, *Int. J. Adv. Biol. Biomed. Res.*, **2022**, *10*, 44-56. [Crossref], [Pdf], [Publisher]
[4] M. Karimi, Considering the main center for treatment and counseling of cancer patients, *Int. J. Adv. Stu. Hum. Soc. Sci.*, **2021**, *10*, 146-150. [Crossref], [Pdf], [Publisher]

[5] Y.F. Mustafa, M.K. Bashir, M.K. Oglah, R.R. Khalil, E.T. Mohammed, Bioactivity of some natural and semisynthetic coumarin derived compounds, *Neuro Quantology*, **2021**, *19*, 129-138. [Crossref], [Google Scholar], [Publisher]
[6] S.A Waheed, Y.F. Mustafa, Synthesis and evaluation of new coumarins as antitumor and antioxidant applicants, *J. Med. Chem. Sci.,* **2022**, *5*, 808-819. [Crossref], [Publisher]
[7] N.T. Abdulaziz, F.Y. Al-bazzaz, Y.F. Mustafa, Natural products for attenuating alzheimer's disease: A narrative review, *Eurasian Chem. Commun.*, **2023**, *5*, 358-370. [Crossref], [Google Scholar], [Publisher]
[8] S.H. Hammoodi, S.S. Ismael, Y.F. Mustafa, Mutual prodrugs for colon targeting: A review, *Eurasian Chem. Commun.*, **2022**, *4*, 1251-1265. [Crossref], [Google Scholar], [Publisher]
[9] W. Chen, R. Zheng, P.D. Baade, S. Zhang, H. Zeng, F. Bray, A. Jemal, X.Q. Yu, J. He, Cancer statistics in China, 2015, *CA. Cancer J. Clin.,* **2016**, *66*, 115–132 [Crossref], [Google Scholar], [Publisher]
[10] A. Oladipupo, C. Alaribe, T. Akintemi, H. Coker, Effect of Phaulopsis falcisepala (Acanthaceae) leaves and stems on mitotic arrest and induction of chromosomal changes in meristematic cells of allium cepa, *Prog. Chem. Biochem. Res.*, **2021**, *4*, 134-147. [Crossref], [Pdf], [Publisher]
[11] L.S. Muhammed, H.T. Sadeq, Using modified resins in chromium ion removal from aqueous solutions, *J. Med. Chem. Sci.*, **2023**, 1862-1871. [Crossref], [Pdf], [Publisher]
[12] S.A Waheed, Y.F. Mustafa, Novel naphthalene-derived coumarin composites: synthesis, antibacterial, and antifungal activity assessments, *Eurasian Chem. Commun.*, **2022**, *4*, 709-724. [Crossref], [Google Scholar], [Publisher]
[13] N.M. Abd Al-Hameed, A.W. Al-Ani, The role of monoamine oxidase and atherogenic index in newly diagnosed and tamoxifen treated women with breast cancer disease, *J. Med. Chem. Sci.*, **2023**, *6*, 645-655. [Crossref], [Pdf], [Publisher]
[14] Z.Q. Mahdi, M.F. Alias, Synthesis and characterization of bulky and nano complexes of telmisartan with some heavy metal ions (Ru3+ and Au3+) and their anticancer activity, *J. Med. Chem. Sci.*, **2023**, *6*, 677-692. [Crossref], [Pdf], [Publisher]
[15] A.T. Jalil, W.T. Mohammad, A. Karevskiy, S.H. Dilfy, Histological diagnosis and staging of cervical cancer samples collected from women in Dhi-Qar province, *J. Med. Chem. Sci.*, **2023**, *6*, 269-279. [Crossref], [Pdf], [Publisher]
[16] M.M. Yaseen, S.A. Alkubaisy, W.T. Mohammad, A.T. Jalil, S.H. Dilfy, Cancer and complications of peptic ulcer in type 2 diabetes mellitus patients at Wasit province, Iraq, *J. Med. Chem. Sci.*, **2023**, *6*, 335-345. [Crossref], [Pdf], [Publisher]
[17] Y.F. Mustafa, Synthesis, characterization, and biomedical assessment of novel bisimidazole–coumarin conjugates, *Appl. Nanosci.,* **2021**, *13*, 1907–1918**.** [Crossref], [Google Scholar], [Publisher]
[18] F. Ugbe, G. Shallangwa, A. Uzairu, I. Abdulkadir, A 2-D QSAR modeling, molecular docking study and design of 2-arylbenzimidazole derivatives as novel leishmania inhibitors: a molecular dynamics study, *Adv. J. Chem. A*, **2023**, *6*, 50-64. [Crossref], [Pdf], [Publisher]
[19] S.F Jasim, Y.F. Mustafa, New fused-coumarin composites: synthesis, anticancer and antioxidant potentials evaluation, *Eurasian Chem. Commun.*, **2022**, *4*, 607-619. [Crossref], [Google Scholar], [Publisher]
[20] N.T Abdulaziz, Y.F Mustafa, The effect of heat variable on the chemical composition and bioactivities of a citrullus lanatus seed aqueous extracts, *J. Med. Chem. Sci.*, **2022**, *5*, 1166-1176. [Crossref], [Google Scholar], [Publisher]
[21] S.A Waheed, Y.F. Mustafa, The in vitro effects of new albocarbon-based coumarins on blood glucose-controlling enzymes, *J. Med.*

Chem. Sci., **2022**, *5*, 954-967. [Crossref], [Pdf], [Publisher]
[22] S. Saedi, A. Saedi, M.M. Ghaemi, M. Milani Fard, 'Pidemiological Study of Breast Cancer in Iran, a review study, *Eurasian J. Sci. Technol.*, **2022**, *2*, 233-241. [Crossref], [Pdf], [Publisher]
[23] Z. Akbarizadeh, G. Najafi, Effect of savory and yarrow on spermatogenesis in adult mice undergoing chemotherapy Cyclosporine, *Int. J. Adv. Biol. Biomed. Res.*, **2016**, *4*, 188-193. [Crossref], [Pdf], [Publisher]
[24] L. Mehrdana, H. Safari, A. Maher, Crisis management in the face of covid-19 to control drug chemistry for cancer patients in different countries: a review study, *J. Chem. Rev.*, **2021**, *3*, 232-246. [Crossref], [Google Scholar], [Publisher]
[25] S.F Jasim, Y.F. Mustafa, Synthesis, ADME study, and antimicrobial evaluation of novel naphthalene-based derivatives, *J. Med. Chem. Sci.*, **2022**, *5*, 793-807. [Crossref], [Google Scholar], [Publisher]
[26] F. Ahmad, M. Mehmood, A critical review of photocatalytic degradation of organophosphorus pesticide "Parathion" by different mixed metal oxides, *Adv. J. Chem. A*, **2022**, *5*, 287-310. [Crossref], [Google Scholar], [Publisher], [Pdf],
[27] Y.F. Mustafa, Classical approaches and their creative advances in the synthesis of coumarins: a brief review, *J. Med. Chem. Sci.*, **2021**, *4*, 612-625. [Crossref], [Google Scholar], [Publisher]
[28] P. Amos, H. Louis, K. Adesina Adegoke, E. A. Eno, A.O. Udochukwu, T. Odey Magub, Understanding the mechanism of electrochemical reduction of CO_2 using Cu/Cu-based electrodes: a review, *Asian J. Nanosci. Mater.*, **2022**, *5*, 252-293. [Crossref], [Google Scholar], [Publisher]
[29] R. Taghavi, S. Rostamnia, Four-component synthesis of polyhydroquinolines via unsymmetrical hantzsch reaction employing Cu-IRMOF-3 as a robust heterogeneous catalyst, *Chem. Methodol.*, **2022**, *6*, 639-648. [Crossref], [Google Scholar], [Publisher]
[30] B. Baghernejad, M. Alikhani, Nano-cerium oxide/aluminum oxide as an efficient catalyst for the synthesis of xanthene derivatives as potential antiviral and anti-inflammatory agents, *J. Appl. Organomet. Chem.*, **2022**, *2*, 155-162. [Crossref], [Google Scholar], [Publisher]
[31] D. Amenu Delesa, Traditional medicinal plants for industrial application as natural food preservatives, *Int. J. Adv. Biol. Biomed. Res.*, **2018**, *6*, 1-10. [Crossref], [Google Scholar], [Publisher]
[32] U. Bello, C.M. Agu, D.A. Ajiya, A.A. Mahmoud, L. Udopia, N.M. Lawal, A.A. Abubakar, M. Muhammad, Biodiesel, in a quest for sustainable renewable energy: a review on its potentials and production strategies, *J. Chem. Rev.*, **2022**, *4*, 272-287. [Crossref], [Google Scholar], [Publisher]
[33] P. Kumar, S. Prasad, D. Yadav, A. Kumar, S. Singh, Variation in dry matter accumulation and crop growth indices due to zinc fertilization of different wheat cultivars under Eastern Indo-Gangatic plain, *Journal of Plant Bioinformatics and Biotechnology*, **2022**, *2*, pp. 44-51. [Crossref], [Pdf], [Publisher]
[34] Y.F. Mustafa, N.A. Mohammed, A promising oral 5-fluorouracil prodrug for lung tumor: synthesis, characterization and releas, *Biochem. Cell. Arch.,* **2021**, *21*, 1991–1999. [Google Scholar], [Pdf], [Publisher]
[35] Y.F. Mustafa, R.R. Khalil, E.T. Mohammed, M.K. Bashir, M.K. Oglah, Effects of structural manipulation on the bioactivity of some coumarin-based products, *Arch. Razi Inst.,* **2021**, *76*, 1297–1305. [Crossref], [Google Scholar], [Publisher]
[36] M.K. Rohmah, O.D. Salahdin, R. Gupta, K. Muzammil, M.T. Qasim, Z.H. Al-qaim, N.F. Abbas, M.A. Jawad, G. Yasin, Y.F. Mustafa, A. Heidary, S. Abarghouei, Modulatory role of dietary curcumin and resveratrol on growth performance, serum immunity responses, mucus enzymes activity, antioxidant capacity and serum and mucus biochemicals in the

common carp, Cyprinus carpio exposed to abamectin, *Fish Shellfish Immunol.,* **2022**, *129*, 221–230. [Crossref], [Google Scholar], [Publisher]

[37] S. Cho, K. Namkoong, M. Shin, J. Park, E. Yang, J. Ihm, V.T. Thu, H.K., J. Han, *J. Med. Food* **2017**, *20*, 323–334. [Crossref], [Google Scholar], [Publisher]

[38] G. Vinodhkumar, R. Ramya, M. Vimalan, I. Potheher, A. Cyrac Peter, Reduced graphene oxide based on simultaneous detection of neurotransmitters, *Prog. Chem. Biochem. Res.,* **2018**, *1*, 40-49. [Crossref], [Google Scholar], [Publisher], [Pdf]

[39] G. Sharma, S.B. Sharma, Synthetic Impatienol analogues as potential cyclooxygenase-2 inhibitors: a preliminary study, *J. Appl. Organomet. Chem.*, **2021**, *1*, 66-75. [Crossref], [Pdf], [Publisher]

[40] V. Tallapaneni, L. Mude, D. Pamu, V.V.S. R. Karri, Formulation, characterization and in vitro evaluation of dual-drug loaded biomimetic chitosan-collagen hybrid nanocomposite scaffolds, *J. Med. Chem. Sci.*, **2022**, *5*, 1059-1074. [Crossref], [Pdf], [Publisher]

[41] Y.F. Mustafa, E.T. Mohammed, R.R. Khalil, Synthesis, characterization, and anticoagulant activity of new functionalized biscoumarins, *Egypt. J. Chem.,* **2021**, *64*, 4461–4468. [Crossref], [Google Scholar], [Publisher]

[42] Y.F. Mustafa, R.R. Khalil, E.T. Mohammed, Synthesis and antitumor potential of new 7-halocoumarin-4-acetic acid derivativesd, *Egypt. J. Chem.,* **2021**, *64*, 3711–3716 [Crossref], [Google Scholar], [Publisher]

[43] M.T. Sheu, H.J. Jhan, C.M. Hsieh, C.J. Wang, H.O Ho, Efficacy of antioxidants as a complementary and alternative medicine (CAM) in combination with the chemotherapeutic agent doxorubicin, *Integr. Cancer Ther.,* **2015**, *14*, 184–195. [Crossref], [Google Scholar], [Publisher]

[44] K. Piska, P. Koczurkiewicz, A. Bucki, K. Wójcik-Pszczoła, M. Kołaczkowski, E. Pękala, Metabolic carbonyl reduction of anthracyclines — role in cardiotoxicity and cancer resistance. Reducing enzymes as putative targets for novel cardioprotective and chemosensitizing agents, *Invest. New Drugs,* **2017**, *35*, 375–385. [Crossref], [Google Scholar], [Publisher]

[45] F. Zhou, , G. Hao, , J. Zhang, , Y. Zheng, , X. Wu, , K. Hao, , F. Niu, , D. Luo, , Y. Sun, , L. Wu, W. Ye, G. Wang, Protective effect of 23-hydroxybetulinic acid on doxorubicin-induced cardiotoxicity: a correlation with the inhibition of carbonyl reductase-mediated metabolism, *Br. J. Pharmacol.,* **2015**, *172*, 5690–5703. [Crossref], [Google Scholar], [Publisher]

[46] Y. Ito, T. Mitani, N. Harada, A. Isayama, S. Tanimori, S. Takenaka, , Y. Nakano, H. Inui, , R. Yamaji, Identification of carbonyl reductase 1 as a resveratrol-binding protein by affinity chromatography using 4'-amino-3,5-dihydroxy-*trans*-stilbene, *J. Nutr. Sci. Vitaminol. (Tokyo).,* **2013**, *59*, 358–364. [Crossref], [Google Scholar], [Publisher]

[47] A. Emadi, S.D. Gore, Arsenic trioxide — an old drug rediscovered, *Blood Rev.,* **2010**, *24*, 191–199. [Crossref], [Google Scholar], [Publisher]

[48] Y.F. Mustafa, N.T. Abdulaziz, Hymecromone and its products as cytotoxic candidates for brain cancer: a brief review, *NeuroQuantology,* **2021**, *19*, 175–186. [Crossref], [Google Scholar], [Publisher]

[49] X.Y. Zhao, G.Y. Li, Y. Liu, L.M. Chai, J.X. Chen, Y. Zhang, Z.M. Du, Y.J. Lu, B.F. Yang, Resveratrol protects against arsenic trioxide-induced cardiotoxicity *in vitro* and *in vivo*, *Br. J. Pharmacol.,* **2008**, *154*, 105–113. [Crossref], [Google Scholar], [Publisher]

[50] A. Ghavamzadeh, K. Alimoghaddam, S. Rostami, S.H. Ghaffari, M. Jahani, M. Iravani, S.A. Mousavi, B. Bahar, M. Jalili, Phase II study of single-agent arsenic trioxide for the front-line therapy of acute promyelocytic leukemia, *J. Clin. Oncol.,* **2011**, *29*, 2753–2757. [Crossref], [Google Scholar], [Publisher]

[51] M. Yu, J. Xue, Y. Li, W. Zhang, D. Ma, L. Liu, Z. Zhang, Resveratrol protects against arsenic trioxide-induced nephrotoxicity by

facilitating arsenic metabolism and decreasing oxidative stress, *Arch. Toxicol.,* **2013**, *87*, 1025–1035. [Crossref], [Google Scholar], [Publisher]

[52] W. Zhang, J. Xue, M. Ge, M. Yu, L. Liu, Z. Zhang, Resveratrol attenuates hepatotoxicity of rats exposed to arsenic trioxide, *Food Chem. Toxicol.,* **2013**, *51*, 87–92. [Crossref], [Google Scholar], [Publisher]

[53] G. Upadhyay, A.K. Singh, A. Kumar, O. Prakash, M.P. Singh, Resveratrol modulates pyrogallol-induced changes in hepatic toxicity markers, xenobiotic metabolizing enzymes and oxidative stress, *Eur. J. Pharmacol.,* **2008**, *596*, 146–152 [Crossref], [Google Scholar], [Publisher]

[54] M.A. Thorat, J. Cuzick, Role of aspirin in cancer prevention, *Curr. Oncol. Rep.* **2013**, *15*, 533–540. [Crossref], [Google Scholar], [Publisher]

[55] A. Dey, P. Guha, S. Chattopadhyay, S.K. Bandyopadhyay, Biphasic activity of resveratrol on indomethacin-induced gastric ulcers, *Biochem. Biophys. Res. Commun.,* **2009**, *381*, 90–95. [Crossref], [Google Scholar], [Publisher]

[56] Y. Zhu, J. Fu, K.L. Shurlknight, D.N. Soroka, Y. Hu, X. Chen, S. Sang, Novel resveratrol-based aspirin prodrugs: synthesis, metabolism, and anticancer activity, *J. Med. Chem.,* **2015**, *58*, 6494–6506. [Crossref], [Google Scholar], [Publisher]

[57] J.L. Ko, C.H. Tsai, T.C. Liu, M.Y. Lin, H.L. Lin, C.C. Ou, Differential effects of grape juice on gastric emptying and renal function from cisplatin-induced acute adverse toxicity, *Hum. Exp. Toxicol.,* **2016**, *35*, 808–817. [Crossref], [Google Scholar], [Publisher]

[58] Y. Ji, L. Cai, T. Zheng, H. Ye, X. Rong, J. Rao, Y. Lu, The mechanism of UVB irradiation induced-apoptosis in cataract, *Mol. Cell. Biochem.,* **2015**, *401*, 87–95. [Crossref], [Google Scholar], [Publisher]

[59] E.T. Mohammed, R.R. Khalil, Y.F. Mustafa, Phytochemical analysis and antimicrobial evaluation of Quince Seeds' Extracts, *J. Med. Chem. Sci.*, **2022**, *5*, 968–979. [Crossref], [Pdf], [Publisher]

[60] N. Skroza, I. Proietti, A. Marchesiello, S. Volpe, V. Balduzzi, N. Bernardini, P. Maddalena, A. Mambrin, S. Michelini, E. Tolino, G. La Torre, C. Potenza, Do diet and lifestyles play a role in the pathogenesis of NMSCs? *Nutrients* **2020**, *12*, 1–7. [Crossref], [Google Scholar], [Publisher]

[61] R.R. Khalil, E.T. Mohammed, Y.F. Mustafa, Evaluation of in vitro antioxidant and antidiabetic properties of cydonia oblonga seeds' extracts, *J. Med. Chem. Sci.*, **2022**, *5*, 1048–1058. [Crossref], [Google Scholar], [Publisher]

[62] W. Al-Shakarchi, N.T. Abdulaziz, Y.F. Mustafa, A review of the chemical, pharmacokinetic, and pharmacological aspects of quercetin, *Eurasian Chem. Commun.*, **2022**, *4*, 645–656. [Crossref], [Google Scholar], [Publisher]

[63] G. Fan, J.J. Tang, M. Bhadauria, S.K. Nirala, F. Dai, B. Zhou, Y. Li, Z.L. Liu, Resveratrol ameliorates carbon tetrachloride-induced acute liver injury in mice, *Environ. Toxicol. Pharmacol.*, **2009**, *28*, 350–356. [Crossref], [Google Scholar], [Publisher]

[64] A. Mandal, D. Bhatia, A. Bishayee, Suppression of inflammatory cascade is implicated in methyl amooranin-mediated inhibition of experimental mammary carcinogenesis, *Mol. Carcinog*., **2014**, *53*, 999–1010. [Crossref], [Google Scholar], [Publisher]

[65] Y.F. Mustafa, Synthesis, characterization and preliminary cytotoxic study of sinapic acid and its analogues, *J. Glob. Pharma Technol.*, **2019**, *11*, 1–10. [Google Scholar], [Publisher]

[66] A.M. Nejres, H.K. Ali, S.P. Behnam, Y.F. Mustafa, Potential effect of ammonium chloride on the optical physical properties of polyvinyl alcohol, *Syst. Rev. Pharm.*, **2020**, *11*, 726–732. [Google Scholar], [Publisher]

[67] A.B. Roomi, G. Widjaja, D. Savitri, A.T. Jalil, Y.F. Mustafa, L. Thangavelu, G. Kazhibayeva, W. Suksatan, S. Chupradit, S. Aravindhan, SnO2:Au/carbon quantum dots

nanocomposites: synthesis, characterization, and antibacterial activity, *J. Nanostructures,* **2021**, *11*, 514–523. [Crossref], [Google Scholar], [Publisher]

[68] J. Dun, X. Chen, H. Gao, Y. Zhang, H. Zhang, Y. Zhang, Resveratrol synergistically augments anti-tumor effect of 5-FU in vitro and in vivo by increasing S-phase arrest and tumor apoptosis, *Exp. Biol. Med.,* **2015**, *240*, 1672–1681. [Crossref], [Google Scholar], [Publisher]

[69] Y.F. Mustafa, Chemotherapeutic applications of folate prodrugs: a review, *NeuroQuantology,* **2021**, *19*, 99–112. [Crossref], [Google Scholar], [Publisher]

[70] O. Komina, J. Wesierska-Gadek, *Biochem. Pharmacol.,* **2008**, *76*, 1554–1562. [Crossref], [Google Scholar], [Publisher]

[71] F. Casanova, J. Quarti, D.C. Ferraz Da Costa, C.A. Ramos, J.L. Da Silva, E. Fialho, Resveratrol chemosensitizes breast cancer cells to melphalan by cell cycle arrest, *J. Cell. Biochem.,* **2012**, *113*, 2586–2596. [Crossref], [Google Scholar], [Publisher]

[72] S.M. Kasim, N.T. Abdulaziz, Y.F. Mustafa, Synthesis and biomedical activities of coumarins derived from natural phenolic acids, *J. Med. Chem. Sci.,* **2022**, *5*, 546–560. [Crossref], [Google Scholar], [Publisher]

[73] X. He, Y. Wang, J. Zhu, M. Orloff, C. Eng, *Cancer Lett.,* **2011**, *301*, 168–176. [Crossref], [Google Scholar], [Publisher]

[74] Y.J. Lee, Y.J. Lee, J.H. Im, S.Y. Won, Y.B. Kim, M.K. Cho, H.S. Nam, Y.J. Choi, S.H. Lee, Synergistic anti-cancer effects of resveratrol and chemotherapeutic agent clofarabine against human malignant mesothelioma MSTO-211H cells, *Food Chem. Toxicol.,* **2013**, *52*, 61–68. [Crossref], [Google Scholar], [Publisher]

[75] J.E. Jee, J. Lim, Y.S. Ong, J. Oon, L. Gao, H.S. Choi Choi, S.S. Lee, An efficient strategy to enhance binding affinity and specificity of a known isozyme inhibitor, *Org. Biomol. Chem.,* **2016**, *14*, 6833–6839. [Crossref], [Google Scholar], [Publisher]

[76] Y.S. Ong, L. Gao, K.A. Kalesh, Z. Yu, J. Wang, C. Liu, Y. Li, H. Sun, S.S. Lee, Recent advances in synthesis and identification of cyclic peptides for bioapplications, *Curr. Top. Med. Chem.,* **2017**, *17*, 2302–2318. [Crossref], [Google Scholar], [Publisher]

How to cite this article: Seema Mahmood Kasim, Noora Thamer Abdulaziz, Mahmood Hashim Jasim, Yasser Fakri Mustafa. Resveratrol in cancer chemotherapy: Is it a preventer, protector, or fighter? *Journal of Medicinal and Pharmaceutical Chemistry Research*, 2023, 5(7), 576-587.