Cancer Nanotechnology

RESEARCH Open Access

Resveratrol-based nano-formulations as an emerging therapeutic strategy for ovarian carcinoma: autophagy stimulation and SIRT-1/Beclin/MMP-9/P53/AKT signaling

Mai O. Kadry[1*]

*Correspondence:
maiosman666@yahoo.com

[1] Therapeutic Chemistry Department, National Research Center, Al Bohouth St, Giza, Dokki, Egypt

Abstract

Background: Resveratrol (RVS) is a stilbene derivative polyphenolic compound extensively recognized for its anti-inflammatory, antioxidant and anti-aging properties, along with its enormous promise in carcinoma treatment. Unfortunately, the oral supplementation of RVS possesses physicochemical and pharmacokinetic constraints that hinder its effects, necessitating the development of suitable administration strategies to improve its effectiveness. As a result, the current study evaluates the use of resveratrol nano-formulations in ovarian cancer therapy. Ovarian cancer was induced in rats using (35 mg/kg BW) 20-Methyl cholanthrene (20-MC) followed by resveratrol and resveratrol nano-formulations therapy for one month.

Results: 20-MC highlighted a noticeable alleviation in autophagy (ATF) biomarkers SIRT-1 and Beclin, inflammatory and apoptotic biomarkers MMP-9, P53 and AKT in addition to oxidative and nitrosative stress biomarkers TAC and NOX and ovarian cancer tumor biomarker CA-125.

Conclusions: Resveratrol and resveratrol nano-formulations modulated autophagy, inflammatory and oxidative stress biomarkers with the upper effect for resveratrol nano-formulations in competing 20-MC-induced ovarian cancer.

Keywords: Resveratrol, Ovarian cancer therapy, Drug-delivery systems, Autophagy

Introduction

Molecular targeted medicine has emerged as a prospective technique for overcoming the defect in specificity of chemotherapy, and nanotechnology emerges as a powerful strategy in this context. For cancer treatment, numerous smart drug delivery technologies, including liposomes or metallic nanoparticles, are currently being employed. Furthermore, there has been a growing emphasis on naturally existing bioactive compounds for chemoprevention and chemotherapy in various types of carcinoma, in addition, there is an obvious concentration on nano-therapy, in which nano-formulations cancer prevention is in an advanced progress (Navya et al. 2019). Alternative nano-formulations

were compared to existing anticancer medications; among other things, they revealed more stability, efficacy, solubility and bio-distribution (Navya et al. 2019). A milestone in carcinoma therapy is the overview of nano-medicine in controlling tumor action and hindering its malignant characteristics. The foremost applications for NPs in carcinoma treatment was diagnosis, cargo delivery (genes or drugs) and non-invasive strategy for malignancy eradication. NPs possess important benefits in carcinoma treatment field, which support its use in oncology, in both clinical and preclinical stages. The advantages of NPs are briefly promoting therapeutic efficacy and reducing cytotoxicity (Dai et Al. 2024). NPs was utilized in phototherapy to enhance singlet oxygen production and hyperthermia for tumor ablation (Wang et al. 2024). NPs, engineered to redesign the tumor microenvironment, revealed prospective outcomes in promoting immunotherapy via immune modulation and targeted delivery by enhancing M1 macrophage polarization, reducing fibroblast activation, encouraging T cell infiltration and promoting dendritic cell maturation (Lu et al. 2024; Li et al. 2024).

ATF cellular machinery involves cytoplasmic substrates degradation in lysosomes via autophagosomes. The frequent elimination of old, damaged and useless cellular molecules via the consecutive translation among amino acids and proteins by protein synthesis, and autophagic protein degradation, aids cellular homeostasis. Developing researches demonstrated that autophagy plays a vital regulatory part in ovarian cancer (OC). Remarkably, microRNAs control gene expression in the posttranscriptional level and consequently can adjust the progression and development of OC via regulating autophagy.

Maturation of autolysosomes occur via the interaction with Beclin1 proteins. After fusion, autolysosomes carry dysfunctional organelles and misfolded proteins that are degraded by lysosomal acid hydrolases for recycling and metabolism in the substrate. Bovine ovarian granulosa cells (BGCs) as a model to elucidate autophagy reflected the role of miRNA-21-3p in bovine ovaries by preventing autophagy in BGCs by hindering AKT/mTOR signaling (Ding et al., 2024).

Polyphenols (PP) are gaining popularity among active natural chemicals because to their high bioavailability and several therapeutic benefits, including anti-inflammatory, antioxidant, anticancer and anti-aging characteristics (Karakaya et al. 2019). In fact, the significance of PP as modulators of oxidative stress in cell carcinoma has received considerable attention. However, with limited stability as a restrictive element, nano-PP is regarded as an effective strategy for overcoming some limitations in safety, targeted power and pharmacokinetics concerns. Among this diverse group of chemicals, resveratrol has sparked significant scientific attention due to its anticancer and antioxidant properties (Summerlin et al. 2015). RVS is a vital antioxidant found in blueberries, peanuts and red grapes (Jeandet et al. 2021).

RVS (3,5,4′-trihydroxy-trans-stilbene) and is a natural stilbenoid. RVS is a phytoalexin, secondary metabolite of plants generated as an adaptive reaction to environmental stressors such as ultra violet irradiation, damage and fungal infections. Resveratrol has shown beneficial chemotherapeutic and chemo-preventive advantages against particular kinds of cancer by virtue of its broad antioxidant action (Oztürk et al., 2017).

RVS interfere with cancer initiates, expansion and progression in tumor microenvironment (Velmurugan et al. 2018 ; Huang et al. 2017). Resveratrol decreases tumor-derived

NOS production, promotes tumor cell apoptosis, suppresses tumor migration and growth and prevents COX action. These detailed procedures have been confirmed in various kinds of cancer (Singh et al., 2013). In fact, the postulated resveratrol's anticancer potential includes pro-apoptotic and anti-proliferative activities and the power to control the expression of tumor suppressor microRNAs, NFκB, nuclear respiratory factor-1 and 2, P53, peroxisome proliferator-activated receptor (PPAR) and pro-oncogenic genes. Although it is exceptional abilities (Zhang et al. 2019), RVS possess restrictions of low water solubility, inadequate oxidative stability and photosensitivity, which severely limit its applicability. As a result, nanotechnology may be an intriguing solution to overcome these constraints (Ahmadi et al., 2019).

In this regard, the present article confers the anticancer machinery of resveratrol and places special highlights on the prospective use of its nano-formulations as a developing cancer remedy, using liposomal nano-delivery systems against 20-MC-induced ovarian cancer while monitoring autophagy and inflammatory pathways.

Material and methods

Chemicals

Liposomal-resveratrol was supplied from Biolife (USA), whereas 20-MA and resveratrol were procured from Sigma-Aldrich Co (St. Louis, MO, USA). SIRT-1 and Beclin RT-PCR kits (Qiagen, USA). MMP-9, AKT and P53 ELISA kits (R&D Systems, USA). All of the chemicals used have a high analytical rank.

Animals and treatments

Western Albino rats (No.40: male) weighing 100–150 g from the National Research Center's animal house have been utilized in the present investigation. The animals were raised under controlled circumstances (22 5 °C, 55% humidity, and a 12-h light/dark cycle). Animals were provided with access to water and a typical diet. All animal care and treatment techniques closely follow to the ethical protocols and policies established by the Animal Care and Use Committee of the National Research Center (19–302) and the US National Institute of Health.

Experimental design

Proceeding acclimatization, animals were put in five cages (8 rats):

G1: Control group administered Tween-80.
G2: Administered 20-methylcholanthrene (IV, 30 mg/kg/10 days for 5 months) (ovarian cancer model)(Lin et al. 2011a).
G3: Administered resveratrol (10 mg/kg BW) IP for 1 month.
G4: Administered liposomal administered (3 mg/kg BW) IP for 1 month (Luo et al. 2013).
G5: Administered Gemzar (10 mg/kg BW) IP for 1 month (standard ovarian cancer drug).

Blood sampling and tissue preparation

Rats were weighed and sedated (with carbon dioxide). After gathering sera from the retro-orbital vein, samples were centrifuged at 5000 rpm for 10 min before being preserved at −80 °C. Rats were euthanized, and ovarian tissue was isolated and homogenized in phosphate buffered saline for further analysis.

Measured biochemical parameters

Ovarian oxidative stress biomarkers

Total antioxidant capacity and nitric oxide were estimated via kits provided from Randox Company. Further, the absorbance was determined spectrophotometry at 505 nm (V-730 UV–visible spectrophotometer-Jasco Inc.) (Abdel-Megeed et al., 2020a).

mRNA gene expression of ovarian SIRT-1 and Beclin

Initially, total RNA was isolated from ovarian tissue using the RNA-easy mini-kit (Qiagen, Germany) and amplified using the RT-PCR kit (Qiagen, USA). The reaction was carried out in a total volume of 20 L of master mix. The thermal profile was as follows: 50 °C for 2 min, 95 °C for 10 min, and 95 °C for 45 to 60 °C for 30 s, 72 °C for 30 s, and 72 °C for 10 min (Agilent, MxPro qPCR, Mx3000P). The ΔΔCT fold change method was used to calculate gene analysis. SIRT-1 and Beclin primers (forward and reverse) illustrated in Table 1 (Kadry et al. 2023b; Abdel-Megeed, et al 2020a, 2020b).

ELISA determination of ovarian CA-125, MMP-9, P53 and P-AKT

The activities of CA-125, MMP-9, P53, and P-AKT were measured using an enzyme-linked immunosorbent assay kit (R&D systems, MN, USA) according to the manufacturer's instructions. The experiment was then evaluated using a quantitative sandwich enzyme immunoassay. The microplate was then pre-coated with the appropriate antibodies. The immobilized antibody that attached to CA-125, MMP-9, P53, and P-AKT was then added, followed by the enzyme-linked secondary antibody specific for CA-125, MMP-9, P53, and P-AKT. The absorbance was then measured at 450 nm. The color intensity (at 450 nm) was measured (Agient BioTek Microplate reader, Neo2) (Kadry and Abdel-Megeed, 2022; Abdel-Megeed et al., 2020b).

Table 1 Primers sequence designed for RT-PCR gene expression

Primer name	Primer sequence
SiRT-1	5′-TGGCAAAGGAGCAGATTAGTAGG-3′ 5′-CTGCCACAAGAACTAGAGGATAAGA-3′
Beclin-1	5′-CTGGACACTCAGCTCAACGTCA-3′ 5′-CTCTAGTGCCAGCTCCTTTAGC-3′
B-actin	5′-GCAGAAGCTGCTGGAGCTGA-3′ 5′-GATCCGGAAGGCGCTGTCT-3′

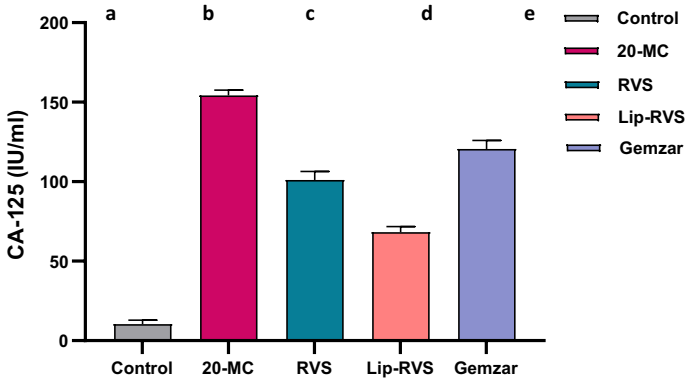

Fig. 1 Impact of resveratrol and liposomal-resveratrol on serum CA-125 post 20-MC-induced ovarian cancer. Data are expressed as means ± SEM ($n = 8$), $P < 0.05$. Groups having different letters are considered significantly different, while, groups having similar letters are not significantly different from each other

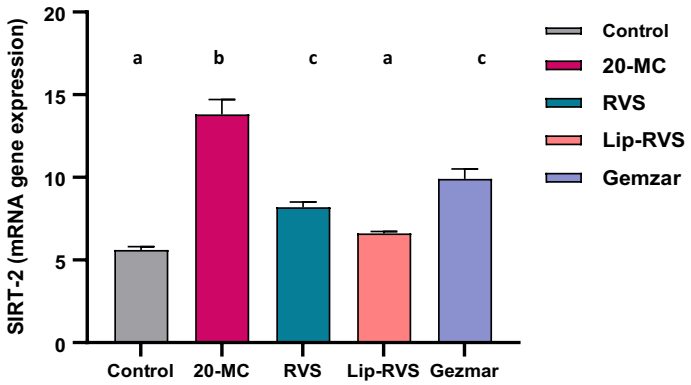

Fig. 2 Impact of resveratrol and liposomal-resveratrol on ovarian SIRT-1 gene expression post 20-MC-induced ovarian cancer. Data are expressed as means ± SEM ($n = 8$), $P < 0.05$. Groups having different letters are considered significantly different, while, groups having similar letters are not significantly different from each other. B-actin was used as reference gene

Statistical analysis

The data were provided in terms of mean standard error of the mean (SEM). For the statistical analysis, GraphPad Instat 3 (GraphPad Software Inc., San Diego, CA, USA) was utilized. SPSS 16 was used to analyze the data using one-way ANOVA, followed by a post hoc Tukey's test. P-values of less than 0.05 were considered statistically significant.

Results

Modulating protein expression of CA-125

The protein expression of the ovarian cancer biomarker CA-125 was dramatically increased by 20-methyl cholanthrene. Meanwhile, resveratrol, liposomal-resveratrol, and Gemzar considerably improved CA-125 protein expression when compared to the control value, with liposomal-resveratrol outperforming the others (Fig. 1).

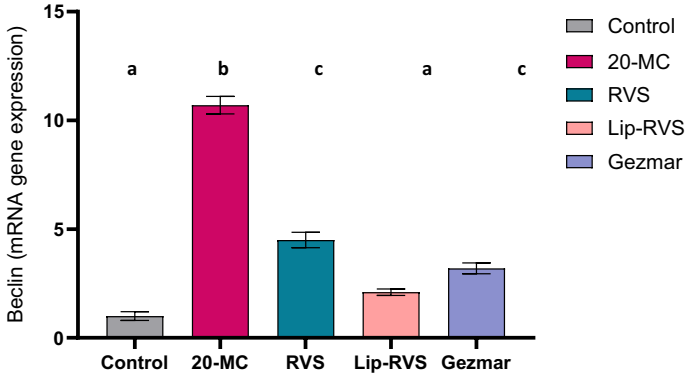

Fig. 3 Impact of resveratrol and liposomal-resveratrol on ovarian Beclin-1 gene expression post 20-MC-induced ovarian cancer. Data are expressed as means ± SEM ($n = 8$), $P < 0.05$. Groups having different letters are considered significantly different, while, groups having similar letters are not significantly different from each other. B-actin was used as reference gene

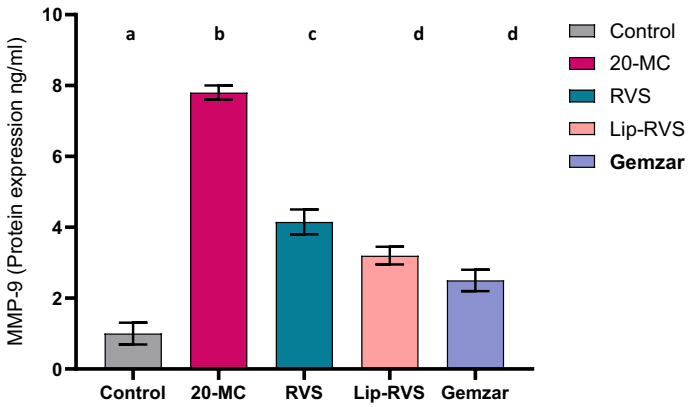

Fig. 4 Impact of resveratrol and liposomal-resveratrol on ovarian MMP-9 protein expression post 20-MC-induced ovarian cancer. Data are expressed as means ± SEM ($n = 8$), $P < 0.05$. Groups having different letters are considered significantly different, while, groups having similar letters are not significantly different from each other

Modulating SIRT-1 and Beclin gene expression

The autophagy biomarkers SIRT-1 and Beclin were dramatically upregulated by 20-methylcholanthrene, indicating endoplasmic reticulum stress. Meanwhile, resveratrol, Liposomal-resveratrol, and Gemzar considerably modified these changed genes when compared to the control, with liposomal-resveratrol having the greatest impact (Figs. 2, 3).

Modulating protein expression of MMP-9, P-AKT and P53

20-Methyl cholanthrene significantly increased MMP-9 protein expression while decreasing P53. Meanwhile, resveratrol, liposomal-resveratrol, and Gemzar greatly improved these changed proteins when compared to the control value, with liposomal-resveratrol outperforming the others (Figs. 4, 5 and 6).

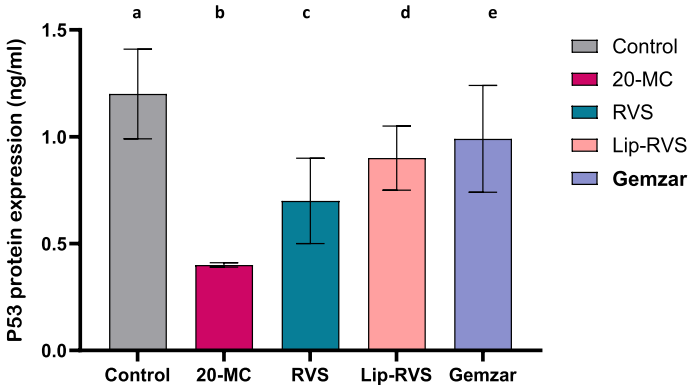

Fig. 5 Impact of resveratrol and liposomal-resveratrol on ovarian P53 protein expression post 20-MC-induced ovarian cancer. Data are expressed as means ± SEM ($n = 8$), $P < 0.05$. Groups having different letters are considered significantly different, while, groups having similar letters are not significantly different from each other

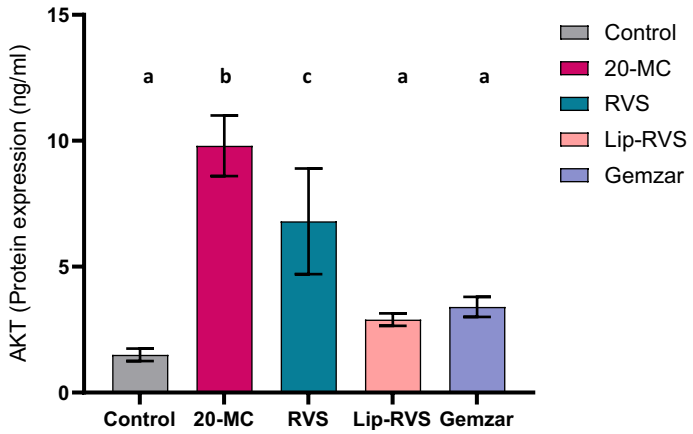

Fig. 6 Impact of resveratrol and liposomal-resveratrol on ovarian AKT-1 protein expression post 20-MC-induced ovarian cancer. Data are expressed as means ± SEM ($n = 8$), $P < 0.05$. Groups having different letters are considered significantly different, while, groups having similar letters are not significantly different from each other

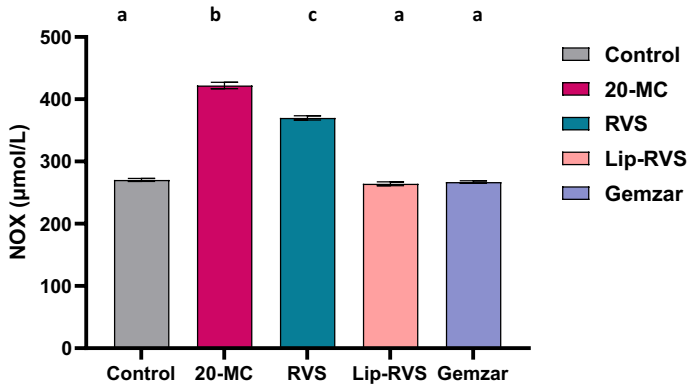

Fig. 7 Impact of resveratrol and liposomal-resveratrol on ovarian NOX level post 20-MC-induced ovarian cancer. Data are expressed as means ± SEM ($n = 8$), $P < 0.05$. Groups having different letters are considered significantly different, while, groups having similar letters are not significantly different from each other

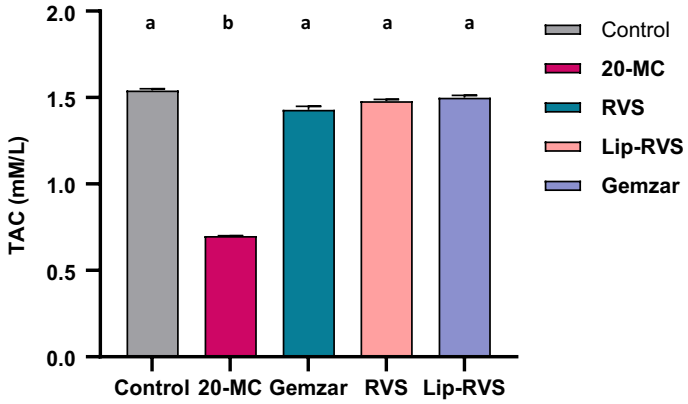

Fig. 8 Impact of resveratrol and liposomal-resveratrol on ovarian TAC level post 20-MC-induced ovarian cancer. Data are expressed as means ± SEM ($n = 8$), $P < 0.05$. Groups having different letters are considered significantly different, while, groups having similar letters are not significantly different from each other

Modulating oxidative stress biomarkers

20-Methyl cholanthrene increased the oxidative stress biomarker NOX while decreasing the anti-oxidative stress biomarker Total antioxidant capacity, indicating an oxidative stress and redox imbalance. Meanwhile, resveratrol, liposomal-resveratrol, and Gemzar considerably modified these changed biomarkers as compared to the control, with liposomal-resveratrol having the greatest impact (Figs. 7, 8).

Discussion

Autophagy is an auto-destructive mechanism that guarantees the survival or promotes the apoptosis of abnormal cells, going ahead the environments of damage, stress and pathogenic poison. Furthermore, autophagy results in the removal of misfolded protein, malfunctional organelles, and the elimination of pathogenic molecules (Elshaer et al. 2018).

Herein, 20-MC elevated autophagy biomarkers including SIRT-1, Beclin and AKT gene expression on the other hand reduced tumor suppressor P53 meanwhile, resveratrol and liposomal-resveratrol modulated these altered genes with the superiority of liposomal-resveratrol. This is consistent with a research conducted on 50 animals treated with 20-MA, in which cystic tumors were developed in 17 cases and solid tumors in 20 cases. The time lapse required for tumor developing was at least 20 weeks, and the longer the observation period, the more tumors generated. After 30 weeks, the development rate of solid tumors was 22.5% (Toshi et al., 1973).

The carcinogen 20-methylcholanthrene (20-MCA) induces cancers in almost all animal species. This chemical is a polycyclic aromatic hydrocarbon (PAH), which has been linked to both animal and human cancers. These compounds are commonly present in the environment, in water, cigarette smoke, food and motor combustion. (20-MCA) is converted enzymatically into a number of metabolites, some of which are reactive. 20-MCA has been employed as a successful animal model in the study of chemoprevention and carcinogenesis in a vast set of enzymes implicated in carcinogenic metabolism. Cell carcinoma is the worldwide cause of mortality globally, and the failure of traditional chemotherapy to significantly reduce mortality suggests that alternative

techniques are urgently needed. Resveratrol's ability to cause autophagy apoptosis by triggering autophagy in apoptotic-deficient cells is a plausible technique for its potential application in cancer treatment. The most prevalent resveratrol signaling pathways involve autophagy induction via enhanced stimulation of MAPK and SIRT1 and hindering Akt/mTOR as noticed in NSCLC. RVS can promote autophagy and accelerate the degradation of p62, as well as inhibit the Nrf2/ARE pathway (Wang et al. 2018). Resveratrol increased PTEN expression while decreased the phosphorylation of AKT in breast cancer. Resveratrol inhibits stromal interaction molecule 1 (STIM1) and inactivates the mTOR pathway in prostate and lung cancers (LCs), whereas it promotes autophagy in colorectal cancer by triggering ROS release and promoting caspases-8 and 3 (Miki et al. 2012; Chang et al. 2017). However, it activates Beclin-1 in ovarian cancer. In conclusion, exaggerated autophagy causes cancer cell apoptosis (Alayev et al. 2015).

RVS has been shown in cellular regulatory mechanisms to induce apoptosis by conjugation with v3 integrin and activating (ERK)1/2 via MAPK-kinase (Elshaer et al. 2018). RVS also interferes in c-Jun and p38 kinases, which has been proven to be the clue in ovarian, breast and prostate carcinoma (Yang et al. 2011). Stimulated ERK1/2 causes P53 phosphorylation in various cell lines for cancer (Lin et al. 2011b), and that RVS can trigger P53-correlated apoptosis. Actually, p53 can be linked to DNA in its activated state and is involved in apoptosis. Furthermore, RVS can increase COX-2 nuclear accumulation via p53-correlated apoptosis in ovarian, and breast cancer (Jang et al. 2022).

In this study, 20-MC increased NOX, MMP, and AKT levels, whereas decreasing TAClevels; resveratrol and liposomal-resveratrol regulated their levels with the superiority of liposomal-resveratrol. Angiogenesis is an essential for cancer progression and growth as cancer cells demand blood vessels for nutrition and oxygen to proliferate and metastasize. Elevation in matrix metalloproteinase (MMP) expression is important for angiogenic process. RVS can decrease endothelial cell migration and adhesion by decreasing MMP-2 and NO action along neo-angiogenesis. This technique is especially useful in chemoprevention. Resveratrol also inhibits the accumulation of HIF-1α and increases thrombospondin-1 (TSP1), a natural inhibitor of angiogenesis (Trapp et al. 2010). NO is involved in cell angiogenesis and proliferation, both can promote tumor metastasis and growth (Trapp et al. 2010).

Metastasis is the mechanism by which cancer cells move to healthy tissues, typically via the lymph or blood. By the way, RVS reduce MMP-9&2, AKT, α-SMA, P-PI3K and Smad-2&3 expressions (Sun et al., 2019). These factors are associated with the TGF-1-induced EMT, and RVS can suppress MDA231 cell migration via EMT. Importantly, tumor invasion and metastasis are linked to the EMT pathway in ovarian cancer (Guarino, 2007).

Resveratrol increased P51 and 53 and α-galactosidase in human NSCLC at a low dose. Thus, the processes by which resveratrol might cause accelerated aging have been linked to an increase in DNA double-strand breaks, ROS generation and reducing GSH (Kumar et al., 2015).

As previously stated, the majority of resveratrol's therapeutic advantages are associated with its anti-inflammatory, antioxidant and neuro-protective properties (Carrizzo et al. 2013).

Nano-medicine are drug delivery systems that is highly being used to counteract the restrictions of drugs instability, poor bioavailability, large dosing requirements, rapid first pass metabolism and poor pharmacokinetics (Mudshinge et al. 2011; Jadhav et al. 2016). NPs encapsulated RVS protects resveratrol from UV light by enhancing bioavailability (Summerlin et al. 2015). On the other hand, liposomal-RVS in nude mice is efficient anti-proliferative agents in brain cancer cells via triggering apoptosis and limiting cell growth. RVS nano-formulation mixed with dequalinium-induced cell death via a mitochondrial pathway in two lung cancer cell lines. Javadi et al. (2018) discovered that liposomal-RVS possess stronger anti-proliferative action and also reduced naked mice tumor formation. Furthermore, the combination of folic acid + RVS-NPs reduced anti-apoptotic (BCL-2 and BCL-XL) genes and NF-kB, COX-2, p65, and pro-apoptotic (BAX and BAK), however a reduction in cancer cells survival rate and promotion in the cleaved caspase-3 expressions were also observed (Singh et al. 2018).

Polymeric NPs-RVS dramatically reduced cell viability in breast and lymph node cancer of the prostate (LNCaP) cells (Wang et al. 2017). Various processes were involved in this example, including apoptosis induction, cell cycle arrest at G1/S, phosphatidyl serine externalization, DNA damage, ROS generation, and mitochondrial membrane potential loss (Nassir et al., 2018; Serini et al. 2018). Casein micelle-RVS significantly reduced cell proliferation, tumor volume and growth biomarkers in breast cancer cells (El-Far et al. 2018). RVS-loaded lipid-core-nano-capsules also inhibited cancer growth in HT29 cells by triggering 36% cell death (Feng et al. 2017a, b). In murine melanoma cells, resveratrol-loaded nano-capsules decreased cell viability, tumor development and inhibited metastasis and lung bleeding (Carletto et al. 2016; Song et al., 2018; Medina-Aguilar et al. 2016). Another study found that encapsulating RVS in an SLN dose-dependent way inhibited proliferation, promoted apoptosis, arrest cell cycle at G0/G1 (Wang et al. 2016) and decreased cyclin D1 level in MDA-MB-231 cancer cells (Jiang et al. 2017; Kadry, 2019). Regardless of encouraging preclinical results, the replication of resveratrol's promise in clinical investigations has been impeded by its limited half-life, low solubility, instability and poor bioavailability. RVS is quickly metabolized to create sulfates and glucuronides thus eliminated in clinical trials (Sanna et al. 2013a, 2013b; Siddiqui et al. 2015; Shindikar et al. 2016). In this regard, various trials were invented to create nano-medicine techniques to accomplish acceptable bioavailability and boost effectiveness in an acceptable dose in order to counteract pharmacokinetic and physicochemical restrictions in clinical studies.

(Guo et al. 2013; Guo et al. 2010 discovered that nano-RVS elevated RVS concentrations in the ovary and delayed ovarian cancer growth in regard to free RVS. Tumor growth was inhibited by free and nano-resveratrol at 46% and 62%, respectively (Guo et al. 2010). Furthermore, the inclusion of resveratrol in SLN resulted in a decrease in cell proliferation, which is advantageous in the prevention of skin cancer. (Teskač and Kristl. 2010) found that resveratrol-SLN had higher solubility, stability, and intracellular delivery.

Sanna et al. (2012) created resveratrol-loaded poly(d,l-lactide-co-glycolide) nanoparticles coated with cationic chitosan (CS-) and anionic alginate (Alg-).

Nanoparticles were effective in delivering RVS in an organized manner. RVS encapsulation provides considerable protection against light-sensitivity, indicating its impact in cancer treatment. When compared to free resveratrol, the impact of nano-RVS on human PC cells resulted in increased cytotoxicity (Sanna et al. 2013b; Nassir et al. 2018). Singh et al. (2017) found that RVS-NPs increased the power of NCI-H160 cells by decreasing the potential of mitochondrial membrane and cell variability while increasing reactive oxygen species, cytotoxicity and DNA mutilation. According to HPLC studies, RVS-NPs had longer half-life and higher bioavailability than RVS (Shangmei et al. 2024).

Conclusion

Nano-resveratrol could be a promising candidate for 20-MCA induced ovarian cancer therapy via regulating autophagy biomarkers (SIRT-1 and Beclin), inflammatory and apoptotic biomarkers (MMP-9, P53 and AKT).

Abbreviations

AKT-1	Serine/threonine kinase-1
ARE	Antioxidant response element
Bax	BCL2 associated X protein
Bcl2	B cell lymphoma 2
MMP-9	Matrix metalloproteinase
NFKB	Nuclear factor kappa-B
P 53	Tumor protein P53
ROS	Reactive oxygen species
STAT-3	Signal transducer and activator of transcription
TNF-α	Tumor necrosis factor-α

Acknowledgements
Gratitude is directed to National Research Center for facilities provided in the examination.

Author contributions
Mai O Kadry: conceived and designed the experiments; shared in performing the experiment; analyzed (biochemical parameters and RT-PCR gene expression) and interpreted the data; contributed reagents, materials, analysis tools or data; wrote the paper.

Funding
Open access funding provided by The Science, Technology & Innovation Funding Authority (STDF) in cooperation with The Egyptian Knowledge Bank (EKB). This work has no financial support.

Availability of data and materials
No additional data or information is available for this paper.

Declarations

Ethics approval and consent to participate
Ethics number is 19302 in our institute (NRC).

Consent for publication
Ethics number is 19302.

Competing interests
The authors declare no conflict of interest.

Received: 29 October 2023 Accepted: 25 June 2024
Published online: 15 July 2024

References

Abdel-Megeed RM, Abd El-Alim SH, Arafa AF, Matloub AA, Farrag AERH, Darwish AB, Abdel-Hamid AZ, Kadry MO (2020a) Crosslink among phosphatidylinositol-3 kinase/Akt, PTEN and STAT-5A signaling pathways post liposomal galactomannan hepatocellular carcinoma therapy. Toxicol Rep 5(7):1531–1541. https://doi.org/10.1016/j.toxrep.2020.10.018.

Abdel-Megeed RM, El Newary SA, Kadry MO, Ghanem HZ, El-Shesheny RA, Said-Al Ahl HAH, Abdel-Hamid AZ (2020b) Hyssopus officinalis exerts hypoglycemic effects on streptozotocin-induced diabetic rats via modulating GSK-3β, C-fos, NF-κB, ABCA1 and ABGA1 gene expression. J Diabetes Metab Disord. https://doi.org/10.1007/s40200-020-00535-y
Ahmadi Z, Mohammadinejad R, Ashrafizadeh M (2019) Drug delivery systems for resveratrol, a non-flavonoid polyphenol: emerging evidence in last decades. J Drug Deliv Sci Technol 51:591–604. https://doi.org/10.1016/j.jddst.2019.03.017
Alayev A, Berger SM, Holz MK (2015) Resveratrol as a novel treatment for diseases with mTOR pathway hyperactivation. Ann N Y Acad Sci 1348:116–123. https://doi.org/10.1111/nyas.12829
Carletto B, Berton J, Ferreira TN, Dalmolin LF, Paludo KS, Mainardes RM et al (2016) Resveratrol-loaded nanocapsules inhibit murine melanoma tumor growth. Colloids Surf B Biointerfaces 144:65–72. https://doi.org/10.1016/j.colsurfb.2016.04.001
Carrizzo A, Forte M, Damato A, Trimarco V, Salzano F, Bartolo M et al (2013) Antioxidant effects of resveratrol in cardiovascular, cerebral and metabolic diseases. Food Chem Toxicol 61:215–226. https://doi.org/10.1016/j.fct.2013.07.021
Chang CH, Lee CY, Lu CC, Tsai FJ, Hsu YM, Tsao JW et al (2017) Resveratrol-induced autophagy and apoptosis in cisplatin-resistant human oral cancer CAR cells: a key role of AMPK and Akt/mTOR signaling. Int J Oncol 50:873–882. https://doi.org/10.3892/ijo.2017.3866
Dai J, Ashrafizadeh M, Aref AR, Sethi G, Ertas YN (2024) Peptide-functionalized, -assembled and -loaded nanoparticles in cancer therapy. Drug Discov Today 16:103981. https://doi.org/10.1016/j.drudis.2024.103981
Ding Y, Huang X, Ji T, Qi C, Gao X, Wei R (2024) The emerging roles of miRNA-mediated autophagy in ovarian cancer. Cell Death Dis. https://doi.org/10.1038/s41419-024-06677-8
El-Far SW, Helmy MW, Khattab SN, Bekhit AA, Hussein AA, Elzoghby AO (2018) Phytosomal bilayer-enveloped casein micelles for codelivery of monascus yellow pigments and resveratrol to breast cancer. Nanomedicine 13:481–499. https://doi.org/10.2217/nnm-2017-0301
Elshaer M, Chen Y, Wang XJTX (2018) Resveratrol an overview of its anticancer mechanisms. Life Sci 207:340–349. https://doi.org/10.1016/j.lfs.2018.06.028
Feng M, Zhong L-X, Zhan Z-Y, Huang Z-H, Xiong J-P (2017a) Enhanced Antitumor efficacy of resveratrol-loaded nanocapsules in colon cancer cells: physicochemical and biological characterization. Eur Rev Med Pharmacol Sci 21:375–382
Feng T, Wei Y, Lee RJ, Zhao L (2017b) Liposomal curcumin and its application in cancer. Int J Nanomed 12:6027–6044. https://doi.org/10.2147/IJN.S132434
Guo L, Peng Y, Yao J, Sui L, Gu A, Wang J (2010) Anticancer activity and molecular mechanism of resveratrol-bovine serum albumin nanoparticles on subcutaneously implanted human primary ovarian carcinoma cells in nude mice. Canc Biother Radiopharm 25:471–477. https://doi.org/10.1089/cbr.2009.0724
Guo W, Li A, Jia Z, Yuan Y, Dai H, Li H (2013) Transferrin modified PEG-PLA-resveratrol conjugates: in vitro and in vivo studies for glioma. Eur J Pharm 718:41–47. https://doi.org/10.1016/j.ejphar.2013.09.034
Huang X, Dai Y, Cai J, Zhong N, Xiao H, McClements DJ et al (2017) Resveratrol encapsulation in core-shell biopolymer nanoparticles: Impact on antioxidant and anticancer activities. Food Hydrocolloids 64:157–165
Jadhav P, Bothiraja C, Pawar A (2016) Resveratrol-piperine loaded mixed micelles: formulation, characterization, bioavailability, safety and in vitro anticancer activity. RSC Adv 6:112795–112805. https://doi.org/10.1039/C6RA24595A
Jang JY, Im E, Kim ND (2022) Mechanism of resveratrol-induced programmed cell death and new drug discovery against cancer: a review. Int J Mol Sci. https://doi.org/10.3390/ijms232213689
Javadi S, Rostamizadeh K, Hejazi J, Parsa M, Fathi M (2018) Curcumin mediated down-regulation of αVβ3 integrin and up-regulation of pyruvate dehydrogenase kinase 4 (PDK4) in Erlotinib resistant SW480 colon cancer cells. Phyther Res 32:355–364. https://doi.org/10.1002/ptr.5984
Jeandet P, Vannozzi A, Sobarzo-Sánchez E, Uddin MS, Bru R, Martínez-Márquez A et al (2021) Phytostilbenes as agrochemicals: biosynthesis, bioactivity, metabolic engineering and biotechnology. Nat Prod Rep 38:1282–1329
Jhaveri A, Deshpande P, Pattni B, Torchilin V (2018) Transferrin-targeted, resveratrol-loaded liposomes for the treatment of glioblastoma. J Control Release 277:89–101. https://doi.org/10.1016/j.jconrel.2018.03.006
Jiang L, Wang W, He Q, Wu Y, Lu Z, Sun J et al (2017) Oleic acid induces apoptosis and autophagy in the treatment of tongue squamous cell carcinomas. Sci Rep 7:11277. https://doi.org/10.1038/s41598-017-11842-5
Kadry MO (2019) Liposomal glutathione as a promising candidate for immunological rheumatoid arthritis therapy. Heliyon. https://doi.org/10.1016/j.heliyon.2019.e02162
Kadry MO, Megeed RMA (2022) Ubiquitous toxicity of mercuric chloride in target tissues and organs: impact of ubidecarenone and liposomal-ubidecarenone STAT 5A/PTEN/PI3K/AKT signaling pathways. J Trace Elem Med Biol 74:127058
Kadry MO, Megeed RMA (2023a) Multipotent stromal stem cell approach in alleviating autophagy Beclin-1/XBP-1/STAT5A/PTEN signaling pathways in Novodrin-induced liver dysfunction. Gene Expr. https://doi.org/10.14218/GE.2023.00052
Kadry MO, Megeed RMA, Abdel M (2023b) Titanium-nanostructured and PEGylated doxorubicin diminish chemotherapeutic resistance in 3-methylcholanthrene renal epithelial cell carcinoma via KRAS/FKBP5/P53/JAK2 signaling. Gene Expr. https://doi.org/10.14218/GE.2023.00069
Karakaya S, Koca M, Yilmaz SV, Yildirim K, Pinar NM, Demirci B et al (2019) Molecular docking studies of coumarins isolated from extracts and essential oils of zosima absinthifolia link as potential inhibitors for Alzheimer's disease. Molecules 24:722. https://doi.org/10.3390/molecules24040722
Kato T, Yakushiji M, Tsunawaki A, Ide K (1973) A study of experimental ovarian tumors produced in rats by the chemical carcinogen, 20- methylcholanthrene. Kurume Med J 20(3):159–167
Li B, Ashrafizadeh M, Jiao T (2024) Biomedical application of metal-organic frameworks (MOFs) in cancer therapy: stimuli-responsive and biomimetic nanocomposites in targeted delivery, phototherapy and diagnosis. Int J Biol Macromol 260(Pt 2):129391. https://doi.org/10.1016/j.ijbiomac.2024.129391
Lin C, Crawford DR, Lin S, Hwang J, Sebuyira A, Meng R et al (2011a) Inducible COX-2-dependent apoptosis in human ovarian cancer cells. Carcinogenesis 32:19–26. https://doi.org/10.1093/carcin/bgq212
Lin HY, Tang HY, Davis FB, Davis PJ (2011b) Resveratrol and apoptosis. Ann N Y Acad Sci 1215:79–88
Lu Q, Kou D, Lou S, Ashrafizadeh M, Aref AR, Canadas I, Tian Y, Niu X, Wang Y, Torabian P, Wang L, Sethi G, Tergaonkar V, Tay F, Yuan Z, Han P (2024) Nanoparticles in tumor microenvironment remodeling and cancer immunotherapy. J Hematol Oncol. https://doi.org/10.1186/s13045-024-01535-8

Luo H, Yang A, Schulte BA, Wargovich MJ, Wang GY (2013) Resveratrol induces premature senescence in lung cancer cells via ROS-mediated DNA damage. PLoS ONE 8:e60065. https://doi.org/10.1371/journal.pone.0060065
Medina-Aguilar R, Marchat LA, Ocampo EA, Gariglio P, Mena JG, Sepúlveda NV et al (2016) Resveratrol inhibits cell cycle progression by targeting aurora kinase a and polo-like kinase 1 in breast cancer cells. Oncol Rep 35:3696–3704
Miki H, Uehara N, Kimura A, Sasaki T, Yuri T, Yoshizawa K et al (2012) Resveratrol induces apoptosis via ROS-triggered autophagy in human colon cancer cells. Int J Oncol 40:1020–1028
Mudshinge SR, Deore AB, Patil S, Bhalgat CM (2011) Nanoparticles: emerging carriers for drug delivery. Saudi Pharm J 19:129–141
Nassir AM, Shahzad N, Ibrahim IAA, Ahmad I, Md S, Ain MR (2018) Resveratrol-loaded PLGA nanoparticles mediated programmed cell death in prostate cancer cells. Saudi Pharm J 26:876–885. https://doi.org/10.1016/j.jsps.2018.03.009[
Navya PN, Kaphle A, Srinivas SP, Bhargava SK, Rotello VM, Daima HK (2019) Current trends and challenges in cancer management and therapy using designer nanomaterials. Nano Converg 6:1–30. https://doi.org/10.1186/s40580-019-0193-2[
Öztürk E, Arslan AKK, Yerer MB, Bishayee A (2017) Resveratrol and diabetes: a critical review of clinical studies. Biomed Pharmacother 95:230–234
Sanna V, Siddiqui IA, Sechi M, Mukhtar H (2013a) Nanoformulation of natural products for prevention and therapy of prostate cancer. Canc Lett 334:142–151. https://doi.org/10.1016/j.canlet.2012.11.037
Sanna V, Siddiqui IA, Sechi M, Mukhtar H (2013b) Resveratrol-loaded nanoparticles based on poly(epsiloncaprolactone) and poly(D, L-lactic-co-glycolic acid)-poly(ethylene glycol) blend for prostate cancer treatment. Mol Pharm 10:3871–3881
Serini S, Cassano R, Corsetto PA, Rizzo AM, Calviello G, Trombino S (2018) Omega-3 PUFA loaded in resveratrol-based solid lipid nanoparticles: physicochemical properties and antineoplastic activities in human colorectal cancer cells in vitro. Int J Mol Sci 19:586. https://doi.org/10.3390/ijms19020586
Shangmei O, Li L, Chenghao Yu, Peng Fu (2024) Natural products' antiangiogenic roles in gynecological cancer. Front Pharmacol 2024:1353056. https://doi.org/10.3389/fphar.2024.1353056
Shindikar A, Akshita SA, Nobre M, Kirolikar S (2016) Curcumin and resveratrol as promising natural remedies with nanomedicine approach for the effective treatment of triple negative breast cancer. J Oncol 4(Suppl 1):421–427
Siddiqui IA, Sanna V, Ahmad N, Sechi M, Mukhtar H (2015) Resveratrol nanoformulation for cancer prevention & therapy. Ann N Y Acad Sci 1348:20–31
Singh CK, George J, Ahmad N (2013) Resveratrol-based combinatorial strategies for cancer management. Ann N Y Acad Sci 1290:113–121
Singh SK, Banerjee S, Acosta EP, Lillard JW, Singh R (2017) Resveratrol induces cell cycle arrest and apoptosis with docetaxel in prostate cancer cells via a p53/p21(WAF1/CIP1) and p27(KIP1) pathway. Oncotarget 8(10):17216–17228
Singh SK, Lillard JW, Singh R (2018) Reversal of drug resistance by planetary ball milled (PBM) nanoparticle loaded with resveratrol and docetaxel in prostate cancer. Canc Lett 427:49–62. https://doi.org/10.1016/j.canlet.2018.04.017
Song Z, Shi Y, Han Q, Dai G (2018) Endothelial growth factor receptor-targeted and reactive oxygen species-responsive lung cancer therapy by docetaxel and resveratrol encapsulated lipid-polymer hybrid nanoparticles. Biomed Pharmacother 105:18–26. https://doi.org/10.1016/j.biopha.2018.05.095
Summerlin N, Soo E, Thakur S, Qu Z, Jambhrunkar S, Popat A (2015) Resveratrol nanoformulations: challenges and opportunities. Int J Pharm 479:282–290
Sun Y, Zhou QM, Lu YY, Zhang H, Chen QL, Zhao M et al (2019) Resveratrol inhibits the migration and metastasis of MDA-MB-231 human breast cancer by reversing TGF-β1-induced epithelial-mesenchymal transition. Molecules 24:1131
Teskač K, Kristl J (2010) The evidence for solid lipid nanoparticles mediated cell uptake of resveratrol. Int J Pharm 390:61–69. https://doi.org/10.1016/j.ijpharm.2009.10.011
Trapp V, Parmakhtiar B, Fruehauf JP (2010) Anti-angiogenic effects of resveratrol mediated by decreased VEGF and increased TSP1 expression in melanoma-endothelial cell co-culture. Angiogenesis 13:305–315
Velmurugan BK, Rathinasamy B, Lohanathan BP, Thiyagarajan V, Weng CF (2018) Neuroprotective role of phytochemicals. Molecules 23:2485
Wang R, Zhang Q, Peng X, Zhou C, Zhong Y, Chen X et al (2016) Stellettin B induces G1 arrest, apoptosis and autophagy in human non-small cell lung cancer A549 Cells via blocking PI3K/Akt/mTOR pathway. Sci Rep 6:27071
Wang W, Zhang L, Chen T, Guo W, Bao X, Wang D et al (2017) Anticancer effects of resveratrol-loaded solid lipid nanoparticles on human breast cancer cells. Molecules 22:1814. https://doi.org/10.3390/molecules22111814
Wang J, Li J, Cao N, Li Z, Han J, Li L (2018) Resveratrol, an activator of SIRT1, induces protective autophagy in non-small-cell lung cancer via inhibiting Akt/mTOR and activating p38-MAPK. OncoTargets Ther 11:7777–7786
Wang Z, Pang S, Liu X, Dong Z, Tian Y, Ashrafizadeh M, Rabiee N, Ertas YN, Mao Y (2024) Chitosan- and hyaluronic acid-based nanoarchitectures in phototherapy: combination cancer chemotherapy, immunotherapy and gene therapy. Int J Biol Macromol 23:132579. https://doi.org/10.1016/j.ijbiomac.2024.132579
Yang R, Zhang H, Zhu L (2011) Inhibitory effect of resveratrol on the expression of the VEGF gene and proliferation in renal cancer cells. Mol Med Rep 4:981–983
Zhang D, Zhang J, Zeng J, Li Z, Zuo H, Huang C et al (2019) Nano-gold loaded with resveratrol enhance the anti-hepatoma effect of resveratrol in vitro and in vivo. J Biomed Nanotechnol 15:288–300. https://doi.org/10.1166/jbn.2019.2682
Sanna V, Roggio AM, Siliani S, Piccinini M, Marceddu S, Mariani A, Sechi M. Development of novel cationicchitosan-and anionic alginate-coated poly(D,L-lactide-co-glycolide) nanoparticles for controlled release andlight protection of resveratrol. Int J Nanomedicine. 2012;7:5501-16. https://doi.org/10.2147/IJN.S36684. Epub 2012 Oct17. PMID: 23093904; PMCID: PMC3477887.

Publisher's Note