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Resveratrol for cancer therapy: Challenges and future perspectives

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ABSTRACT

Resveratrol (3,4',5-trihydroxy-trans-stilbene) has been expected to ameliorate cancer and foster breakthroughs in cancer therapy. Despite thousands of preclinical studies on the anticancer activity of resveratrol, little progress has been made in translational research and clinical trials. Most studies have focused on its anticancer effects, cellular mechanisms, and signal transduction pathways *in vitro* and *in vivo*. In this review, we aimed to discern the causes that prevent resveratrol from being used in cancer treatment. Among the various limitations, poor pharmacokinetics and low potency seem to be the two main bottlenecks of resveratrol. In addition, resveratrol-induced nephrotoxicity in multiple myeloma patients hinders its further development as an anticancer drug. New insights and strategies have been proposed to accelerate the conversion of resveratrol from bench to bedside. In the interim, the most promising approach is to enhance the bioavailability of resveratrol with new formulations. Alternatively, more potent analogues of resveratrol could be developed to augment its anticancer potency. Given all the gaps mentioned, much work remains to be done. However, if remarkable progress can be made, resveratrol may finally be used for cancer therapy.

1. Introduction

Resveratrol (3,4',5-trihydroxy-trans-stilbene), is a "miracle" nutraceutical with promise to ameliorate cancer and herald breakthroughs in cancer therapy. As a natural phytoalexin, resveratrol is produced by plants to protect them from environmental stress and pathogenic invasion [1]. It was first isolated in 1940 from the roots of *Veratrum album* (white hellebore) and later extracted from the roots of the plant *Polygonum cuspidatum* (Japanese Knotweed) in 1963 [2]. Although its cardioprotective benefits were first claimed in 1982 [3], it was only after 1992, when the resveratrol contained in red wine was suggested to confer cardioprotective health benefits [4], that the compound became popular [5]. When topical resveratrol was reported to prevent tumorigenesis in a mouse skin cancer model in 1997, its possible use as a novel anticancer drug was highlighted [6].

Resveratrol can be extracted from more than 70 plants [7]. It is present in natural foods like peanuts and pistachios, and in lower amounts in bilberries and blueberries. It is commonly detected and

Abbreviations: ALT, alanine aminotransferase; AMPK, AMP-activated protein kinase; AST, aspartate transaminase; Cmax, maximum serum concentration; IC_{50}, half maximum inhibitory concentration; IGFBP-3, insulin-like growth factor-binding protein 3; IGF-1, insulin-like growth factor-1; MCP1, monocyte chemoattractant protein-1; MPX, muscadine grape extract; PGE2, prostaglandin-E2; RASSF-1a, Ras-association domain family-1a; Tmax, time to maximum serum concentration; TNF-α, tumour necrosis factor alpha; Vd, volume of distribution; VEGF, angiogenic vascular endothelial growth factor; Wnt, wingless-related integration site.

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extracted from grapes [8], whose skin is particularly rich in resveratrol content, and present in wine. Raw cranberry juice, chocolate, and cocoa powder-containing products also contain resveratrol [9]. Resveratrol exists as two geometrical isomers. Its *cis*-isomer is unstable, and is thus unavailable commercially. Its *trans*-isomer possesses greater stability but converts to the *cis*-isomer under exposure to high pH or UV light [10], with heat accelerating the degradation process [11]. Apart from the greater stability and biological activity of the *trans*-isomer as compared to the *cis*-isomer [12], the former is believed to be responsible for the anticancer and health benefits of resveratrol. Therefore, the research has focused on the therapeutic application of its *trans*-isomer.

Resveratrol has an inexhaustible list of health benefits, from boosting immunity, slowing aging processes, and mimicking the effects of calorie restriction, which lead to its anti-obesity effects, to specific actions that prevent or alleviate diseases such as diabetes as well as neurodegenerative and cardiovascular diseases [13]. Most importantly, extensive research has reiterated its suppressive role on cancer [14]. Resveratrol acts as a chemopreventive agent in the four major stages of carcinogenesis, namely initiation, promotion, progression, and metastasis [6], and has also shown efficacy for cancer treatment *in vitro* and *in vivo* [15]. With its antioxidant, anti-inflammatory, and direct anti-tumour properties, resveratrol holds great potential as a complementary agent to conventional chemotherapy [16]. To date, it has shown efficacy against obesity-associated cancers such as hepatic, pancreatic, postmenopausal breast, prostate, and colorectal cancer [17] as well as lung [18], skin [19] and haematological malignancies [20]. Multiple reviews have summarised the various mechanisms and pathways whereby resveratrol exerts its effects [21–27], which are shown in Fig. 1. Previous research

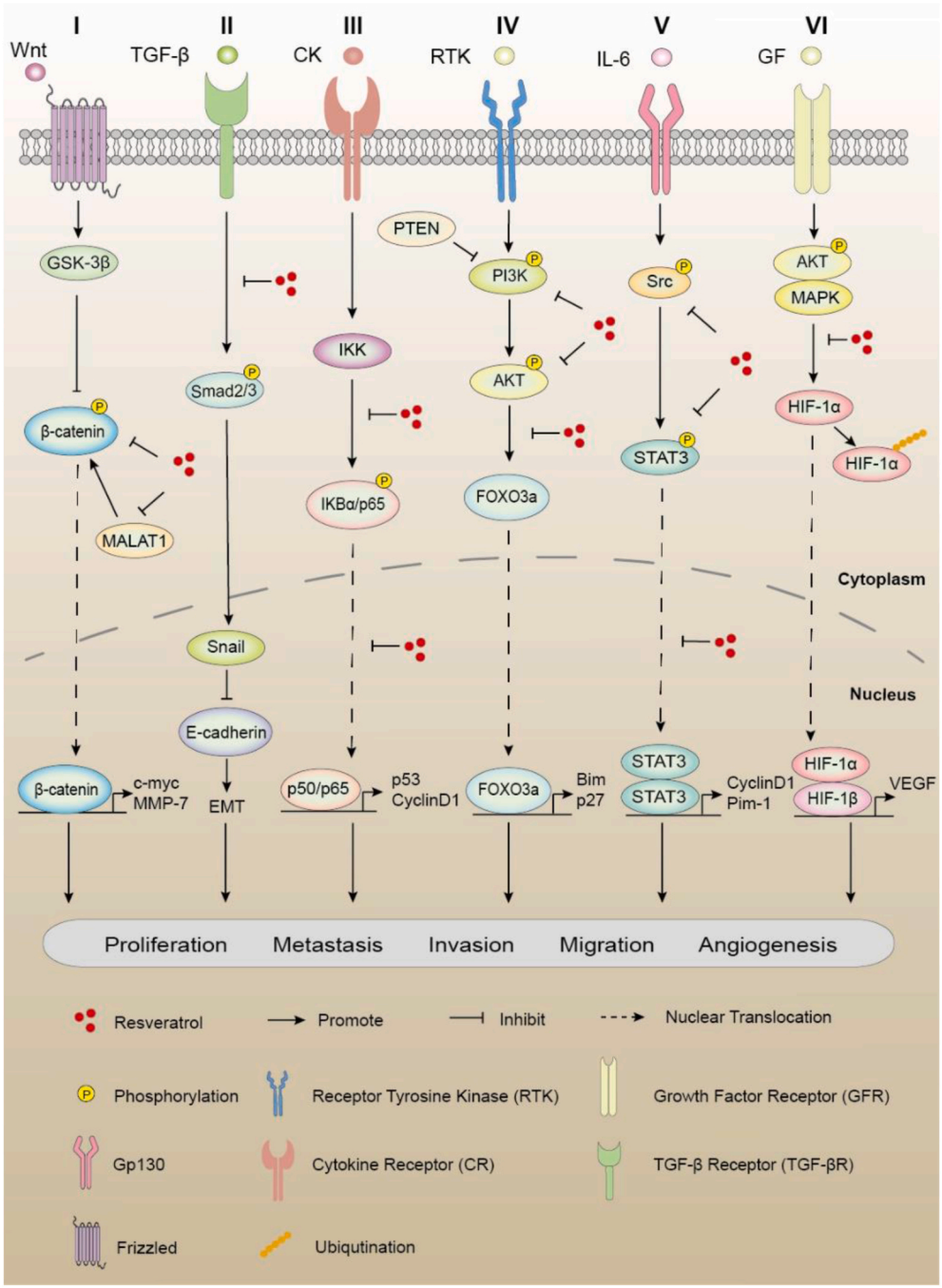

Fig. 1. Schematic representation of the different signalling pathways that are targeted using resveratrol as a novel therapeutic strategy for cancer treatment.

showed that resveratrol exerts its anti-tumour effects via pleiotropic mechanisms rather than a single mechanism of action [28]. Its ability to act on multiple nodes in tumour carcinogenesis has contributed to its usefulness as a combination agent with other therapies, where it synergises with their chemotherapeutic effects [29,30], or sensitizes [31,32] resistant tumour cells to cytotoxicity [33,34]. Additionally, resveratrol protects healthy cells from the adverse effects of conventional agents [32], including xerostomia and mucositis [35]. Thus, its potential utility as an anticancer agent is extremely attractive. Despite all the reported benefits, resveratrol has made only marginal progress in cancer therapy. It is currently unclear why the clinical translation of such a miraculous nutraceutical, which has shown enormous potential preclinically, has been stagnated after animal studies. As such, this review seeks to explore the bottlenecks in its clinical translation as a therapeutic agent against cancers (e.g., colorectal cancer). We aim to highlight the specific challenges that are being faced through a critical evaluation of the currently available data from preclinical and clinical studies, with a special emphasis on several crucial aspects such as pharmacokinetic parameters, its potency in killing cancer cells, and its toxicity profile.

(I) Resveratrol downregulates the expression of β-catenin and blocks β-catenin nuclear translocation through perturbation of the long non-coding RNA MALAT1; (II) it suppresses TGF-β/Smad-induced epithelial-mesenchymal transition (EMT) and transcription factor Snail; (III) it lowers the expressions of IKK-induced TNF-β, leading to the inhibition of cancer cell proliferation through deactivation of NF-ķB; (IV) it inhibits p-PI3K/p-AKT-mediated FOXO3a nuclear accumulation; (V) it suppresses the phosphorylation of Src-STAT3 and induces apoptosis of cancer cells; (VI) it inhibits AKT/MAPK-induced HIF-1α activation and accelerates the degradation of the HIF-1α protein via ubiquitination.

2. Methods

The references were searched and retrieved from PubMed. A preliminary search using the word "resveratrol" generated over 12,000 results. Therefore, a 2-fold search strategy was adopted to reduce the number of results, which consisted in: a primary search to identify studies related to cancer using "resveratrol (MeSH Terms) and cancer (MeSH Terms)"; a second search using "resveratrol (MeSH Terms) and neoplasms (MeSH Terms)" (Fig. 2).

Duplicates were screened using EndNote®. Then, titles and abstracts were screened, and studies were excluded if they did not meet the inclusion criteria. The remaining studies were further sorted into three categories: reviews, preclinical/non-cancer studies, and clinical trials. Each category was then further screened to identify those studies with relevant pharmacokinetic parameters and the eligibility for inclusion of the full texts was assessed. Supplementary searches were performed when necessary to retrieve additional information. To comply with the reference limit (less than 100) required by Cancer Letters for mini-review paper, those not that relevant preclinical/non-cancer studies were also excluded.

3. Pharmacokinetics and efficacy studies of resveratrol for chemoprevention and cancer treatment

Despite its promising efficacy in preclinical studies, the efficacy of resveratrol has not been clearly established in human subjects due to poor pharmacokinetic properties and low potency. A crucial point is to note the difference between chemoprevention and chemotherapy because, although they overlap to some extent, they constitute different paradigms and require different doses for efficacy [36].

3.1. Chemopreventive studies

Boocock et al. [37] attempted to define the dose-dependent pharmacokinetics of resveratrol by giving increasing single doses of 0.5 g, 1 g, 2.5 g, and 5 g to healthy volunteers. However, only a maximum serum concentration (Cmax) of 2.40 μM and a time to maximum serum concentration (Tmax) of 1.5 h was attained with the highest dose (5 g). Although this Cmax is substantially high, it does not reach the half maximum inhibitory concentration (IC_{50}) values required for most

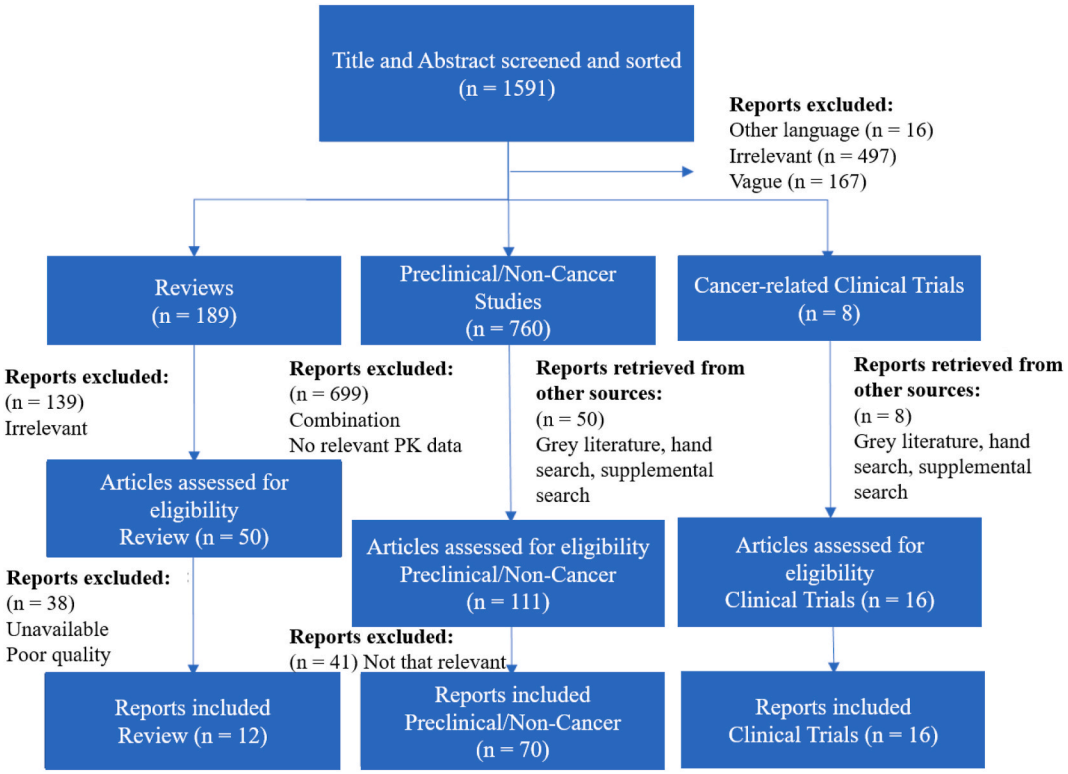

Fig. 2. Primary search strategy for preclinical and clinical studies involving cancer.

cancer cells in cell culture systems (5.0–100.0 μM). The low Cmax of resveratrol may be mainly due to its rapid metabolism rather than to poor water solubility. On the other hand, resveratrol has been shown to bind extensively (97.6%) and tightly to human serum albumin with an affinity association constant of $K = 2.56 \times 10^5\ M^{-1}$ [38]. This greatly facilitates its accessibility to body tissues including tumour tissues, leading to a large volume of distribution (Vd = 9198–22226 L) [37]. In a similar study by Brown et al. [39], the dose-dependent pharmacokinetics of multiple doses for a total of 29 days was tested, and a Cmax of 4.24 μM was obtained for resveratrol after repeating 5 g doses, which is approximately 2-fold higher than that obtained in the previous study with an equivalent single dose. Thus, a multiple dosing regimen with resveratrol may be more appropriate.

Apart from reporting the pharmacokinetic parameters of resveratrol, numerous studies have also examined its effect on important cancer biomarkers. Resveratrol was shown to suppress plasma insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-binding protein 3 (IGFBP-3), which are proteins of the insulin signalling pathway responsible for tumorigenesis [39]. Interestingly, the most pronounced reduction in IGF-1 expression was observed with the 2.5 g/day, rather than the 5 g/day, dose arm. IGFBP-3 expression was reduced in the 1 g/day and 2.5 g/day arms, but not in the 5 g/day arm of healthy volunteers. This could be suggestive of a non-linear dose response relationship or a hormetic effect, which would make precise dosing and titration crucial for efficacy. Zhu et al. [40] administered 50 mg resveratrol twice daily for 12 weeks, achieving mean plasma resveratrol levels below 5.0 μM (2.9 μM), but demonstrating an effect on cancer biomarkers, with a decrease in Ras-association domain family-1a (RASSF-1a) methylation and prostaglandin-E2 (PGE2) expression, which was linked with antiproliferative and anti-inflammatory effects. Meanwhile, Espinoza et al. [41] achieved mean resveratrol plasma levels below the 5.0 μM cut-off with 1 g/day, but the administration of resveratrol was associated with a significant upregulation of immunomodulatory T-cell levels, the downregulation of proinflammatory cytokines such as tumour necrosis factor alpha (TNF-α) and monocyte chemoattractant protein-1 (MCP1), and greater plasma antioxidant activity compared to baseline. Evaluating resveratrol in mixed formulations, Holocombe et al. [42] reported that milligram doses of resveratrol from grapes inhibited wingless-related integration site (Wnt)-signalling, which had an anti-proliferative effect. Moreover, Nguyen et al. [43] reported a noticeable decrease in Wnt target genes and stem cell markers in normal colonic mucosa. Overall, based on its effects on selected tumour markers, it appears that low doses of resveratrol, though only achieving plasma concentrations below the IC_{50} for cytotoxicity, do indeed have a chemopreventive capacity.

Apart from investigating the pharmacokinetics and pharmacodynamics of the parent compound, several studies have also reported the pharmacokinetics of resveratrol metabolites. Remarkably, the plasma concentrations of these metabolites were much higher than those of the parent drug. In the study by Boocock et al. [37], resveratrol-3-O-sulfate showed the highest Cmax, followed by resveratrol-3-O-glucuronide and resveratrol-4′-O-glucuronide. The AUCs of resveratrol-3-O-sulfate and resveratrol-glucuronide were 10- to 20-fold and 4- to 7-fold higher, respectively, than that of resveratrol. In the study by Brown et al. [39], the resveratrol-3-O-sulfate Cmax at the highest 5 g/day dose was 14.0 μM, while that of resveratrol glucuronides was 4.30 μM. Chow et al. [44] measured plasma resveratrol and metabolite concentrations within an hour following a single 1 g dose, and found that the mean plasma concentrations for parent resveratrol were lower than its IC_{50} for anticancer activity; however, resveratrol metabolites reached higher concentrations than the parent compound. Once more, resveratrol-3-sulfate showed the most promising plasma concentrations (mean = 7.7 μM, Cmax = 36.0 μM). Given the significantly higher accumulation of metabolites, especially resveratrol-3-sulfate, it may be worth exploring whether resveratrol metabolites have any therapeutic effects on both cell cytotoxicity and attenuation of important proteins involved in tumorigenesis.

3.2. Chemotherapeutic studies in human subjects

Howells et al. [45] administered SRT501 (5 g/day), a micronized resveratrol formulation, to colorectal cancer patients for 10–21 days. In SRT501, particle size was reduced to enhance bioavailability by increasing surface area and improving suspension properties. SRT501 attained a Cmax = 8.51 μM, which is within the lower end of the postulated efficacious IC_{50} range. The Cmax of the SRT501 formulation was 3-fold higher than that achieved by a single dose of non-micronized resveratrol [37]. The mean resveratrol level in tumour tissues was 4.81 nmol/g for SRT501. These encouraging results suggest that micronized formulations could be utilized to improve the bioavailability of resveratrol.

When Cai et al. [46] administered 1 g/day doses of pure ^{14}C-labelled resveratrol to colorectal cancer patients for six days, the total resveratrol level in malignant tumour tissue ranged from 3.0 to 376.0 nmol/g. Even higher concentrations were detected in non-malignant colonic mucosa and muscle tissue. Patel et al. [47] also reported that resveratrol accumulated in colonic tissue in a non-linear dose-response manner, and could reach levels as high as 674.00 nmol/g and 18.60 nmol/g after doses of 1 g/day and 0.5 g/day, respectively, for 8 days.

Howells et al. [45] demonstrated a marked increase in the expression of cleaved caspase-3, which is a marker of apoptosis, in tumour tissue after treatment with pure resveratrol (5 g/day for two weeks). However, no significant effects in the anti-inflammatory marker prostaglandin-E2 (PGE2) or angiogenic vascular endothelial growth factor (VEGF) were observed. This study demonstrated the apoptotic potential of resveratrol when given for two weeks at 5 g/day, but the treatment did not demonstrate any anti-inflammatory or anti-angiogenic effects. Intriguingly, Cai et al. [46] found that resveratrol at a much lower dose of 5 mg/day positively elevated oxidative stress biomarkers in colorectal tumour tissue and activated maximal autophagy and AMP-activated protein kinase (AMPK). However, these effects were not observed at the 1 g/day dose, reiterating the possibility of a hormetic dose response. Therefore, it is essential to further define the specific efficacious doses.

Patel et al. [47] tested the administration of pure resveratrol at 0.5 g/day and 1 g/day for 8 days to colorectal cancer patients. Although the plasma concentrations of parent resveratrol were undetectable after the last dose, several metabolites were detected, of which resveratrol-sulfate-glucuronide showed the highest concentration (13.4 μM and 22.3 μM after 0.5 and 1 g/day doses, respectively). The plasma levels of resveratrol-3-O-sulfate and resveratrol monoglucuronides were detectable but did not reach micromolar concentrations at 1 g/day doses. On the other hand, the metabolites were highly concentrated in tissues. The highest concentrations were observed with resveratrol-3-O-sulfate (67.2 nmol/g after 1 g/day doses) and resveratrol-3-glucuronide (86.0 nmol/g after 0.5 g/day doses). Similar to findings by Cai et al. [46], it appeared that the area proximal to the tumour on the right colon accumulated the most resveratrol, either as the parent compound or as metabolites. Overall, the high concentrations in colonic tissue met the required *in vitro* resveratrol IC_{50}, making it a feasible agent for colorectal cancer treatment. Current data also point towards the possibility of concentration-dependent biotransformation. At lower doses [37,48], glucuronides were the dominant metabolites, whereas at higher doses [37,39], sulphates, 3-O-sulfate particularly, were the main metabolites. A plausible metabolic pathway for resveratrol has glucuronidation as the first step, and after saturation, sulfation as the second step, which could explain why the concentrations obtained by Patel et al. [47] depended on the doses employed, and why the metabolites contributing to the effect, if any, will vary depending on type of metabolites and the tumor tissue concentrations available.

Resveratrol was also tested in combination with other constituents. Ávila Gálvez et al. [48] examined the administration of a dietary plant extract blend consisting of ~161.6 mg resveratrol/day, and only

achieved nanomolar concentrations of resveratrol in plasma. Though these milligram doses were too low to give meaningful concentrations, both resveratrol and its metabolites concentrated more in malignant than normal tissues, possibly due to is lipophilic nature, suggesting that resveratrol and its metabolites are likely more useful for the treatment of obesity-related cancers. Nguyen et al. [43] also reported that low milligram doses of resveratrol delivered as resveratrol/quercetin tablets or as a grape seed extract blend did not significantly inhibit the Wnt pathway in malignant colonic tissue.

Paller et al. [49] evaluated the efficacy of low microgram doses of pulverized muscadine grape extract (MPX) capsules as a therapeutic option for biochemically recurrent prostate cancer patients for 28 days in the first study and for 12 months in the second study [50]. For the first study, both low dose (500 mg) and high dose (4000 mg) MPX are safe. In the 12 months of treatment, prostate-specific antigen doubling time (PSADT), which is indicative of disease progression, was unchanged, ascertaining that microgram doses are below the threshold for therapeutic effects even with long term administration. Van Die et al. [51] tested a blend containing a higher dose of resveratrol (30 mg) in a similar patient group, and also reported an insignificant lengthening in PSADT. It is important to note that low doses were used in the study, explaining the lack of effect, and that much higher doses may be needed for chemotherapeutic efficacy. Additionally, it is currently unknown whether the other constituents in the formulation influenced the pharmacokinetic profile of resveratrol. Follow-up studies using pure resveratrol at higher doses in a similar group of patients would be valuable.

Ávila Gálvez et al. [48] further described a resveratrol blend that led to the production of phenolic metabolites, predominantly glucuronidated and sulphated, in both malignant (85.5%) and normal (86.6%) tissues. Resveratrol-3-O-glucuronide showed the highest recorded levels, followed by resveratrol-3-O-sulfate.

4. Toxic effects of resveratrol

4.1. In healthy populations

The incidence and severity of toxic effects depend on the dosage of resveratrol and duration of treatment. At single doses of less than 1 g, there are little or no drug-related adverse events (Table 1). Mild and transient adverse events such as diarrhoea, nausea, vomiting, flatulence, abdominal cramps, headache, and rash [52] have been reported with doses greater than 0.5 g/day for a month. In the study by Brown et al. [39], gastrointestinal side effects were dose-dependent, with only doses higher than 2.5 g displaying side effects. Overall, resveratrol is generally considered to be well-tolerated at doses below 1 g/day.

Resveratrol intake at 1 g/day was assessed in overweight or obese postmenopausal women for 12 weeks [53]. In this study, six subjects withdrew due to intolerance and one reported asymptomatic grade 4 alanine aminotransferase (ALT) and aspartate transaminase (AST)

Table 1
Side effects of resveratrol in chemopreventive and chemotherapeutic clinical trials.

Phase	Tumour Type	Subjects	Formulation	Dose/Duration	Safety	References
Chemopreventive Studies						
I	Breast cancer prevention	39 (postmenopausal)	Oral res	5, 50 mg BD 12 weeks	–	[40]
II	General Chemoprevention	40 (healthy)	Oral res	0.5, 1.0, 2.5, 5 g OD 29 days	GI related side effects with 2.5 g and 5 g doses	[39]
I	General Chemoprevention	40 (healthy)	Oral res	0.5, 1.0, 2.5, 5 g OD Single dose	No side effects, one patient experienced raised bilirubin	[37]
I	General Chemoprevention	42 (healthy)	Oral res	1 g QD 4 weeks	Mild transient side effects	[60]
I	Breast cancer prevention	40 healthy (postmenopausal)	Oral res	1 g OD 12 weeks	GI side effects leading to withdrawal	[53]
I	General Chemoprevention	9 (healthy)	Oral res	1 g OD 28 days	Mild GI side effects	[41]
I	Colon Cancer prevention	30 (healthy)	Grapes	0.15, 0.30, 0.45 kg OD (~7.5, 15, 22.5 mg res)* 2 weeks	No side effects	[42]
Chemotherapeutic Studies						
I	Colorectal	8 (patients)	Oral res (Tablet/ Grape Powder)	0.89, 15.54 mg OD (oral resveratrol) 0.07, 0.11 mg (grape powder) 2 weeks	No side effects	[43]
I	Colorectal	24 (patients)	Oral res	5 mg, 1 g OD 6 days	–	[46]
I	Colorectal	20 (patients)	Oral res (tablet)	0.5, 1 g OD 8 days	No side effects	[61]
I	Colorectal cancer, Hepatic Metastases	9 (patients)	Oral res (SRT501 pure micronized res)	5 g OD 14 (10–21 days)	Mild, gastrointestinal side effects	[45]
I	Breast	19 (patients)	Oral res (Blend: 53.85 mg res/ 700 mg)	161.55 mg OD 6 ± 2 days	–	[48]
I/II	Prostate	14 (patients)	Oral res (MPX: 4.4 μg res/ capsule)	8.80, 17.60, 26.40, 35.20 μg res OD (1, 2, 3, 4 g) 28 days	Mild, gastrointestinal side effects in the highest dose group	[49]
II	Prostate	125 (patients)	Oral res (MPX: 4.4 μg res/ capsule)	4.40, 35.20 μg res OD (0.5 g, 4 g) 12 months	Mild to moderate nondrug-related side effects (only one confirmed with drug-related gastrointestinal side effects in the high-dose group)	[50]
I	Prostate	22 (patients)	Oral res (Blend: ~30 mg res/day)	~30 mg OD (in BD doses) 12 weeks	Mild to moderate nondrug-related side effects	[51]
II	Multiple Myeloma	24 (patients)	Oral res (SRT501 pure micronized res)	5 g OD 5 g OD with Bortezomib 21 days (up to 12 cycles)	Renal toxicity led to termination of study only in patients taking resveratrol alone. Five developed renal failure evidenced by elevated serum creatinine; cast and crystal nephropathy (n = 1), acute tubular damage w/o cast nephropathy (n = 1)	[56]

Abbreviations: res: resveratrol; GI: gastrointestinal; OD: once daily; BD: twice daily;

elevations, which could be drug-related. Another study reported a single episode of slightly elevated blood bilirubin and ALT, which resolved within a week without complications [37]. Yet, a study showed no raise in bilirubin levels after 1 g/day administration for four weeks [44]. Hepatotoxicity cannot be ruled out and it warrants further investigation. Rare dyslipidaemia was also reported, but the exact effects of resveratrol on serum lipids are unclear [44]. A recent study showed that doses up to 2 g/day for four weeks did not influence lipid profiles in overweight or obese glucose-intolerant elderly [54], whereas another study showed that resveratrol had in fact a positive effect on the lipid profile, raising the HDL levels in diabetics [55].

4.2. In diseased subjects

Popat et al. [56] showed that the administration of 5 g/day doses resulted in unexpected renal toxicity in five multiple myeloma patients, leading to premature termination. This contrasts with earlier trials supporting the safety of resveratrol. Howells et al. [45] did not report any nephrotoxicity in metastatic colorectal cancer patients administered with SRT501 at 5 g/day for 14 days. In fact, the original formulation resulted in severe gastrointestinal symptoms at a dose greater than 2.5 g [39], while micronized resveratrol was more well-tolerated. Thus, nephrotoxicity may not be formulation-related but disease-induced, with renal impairment being a common complication in up to 50% of multiple myeloma patients [57]. Renal failure was only observed for those subjects taking SRT501 as monotherapy, while subjects on both SRT501 and bortezomib were spared. The low efficacy of SRT501 in the absence of disease stabilization support from bortezomib, together with nausea and vomiting as side effects, may have resulted in the observed dehydration in patients on monotherapy. This possibly exacerbated disease progression and precipitated renal failure, highlighting that the medical conditions of subjects need to be scrutinized in order to reinforce the safety of resveratrol in diseased states. Cancer patients tend to have multiple comorbidities, subsequently lowering their drug toxicity thresholds, and may thus be more susceptible to risks for toxicity and adverse effects.

Yiu et al. [58] demonstrated dose-dependent gastrointestinal side effects in a trial on Friedreich's Ataxia patients, where 71.0% suffered from diarrhoea and 86.0% experienced loose stools in the high-dose 2.5 g arm. Seven subjects with moderate to severe diarrhoea had to be treated with loperamide, and four subjects in the high-dose arm had their dose reduced due to intolerance. Likewise, in the study by La Porte et al. [52], where a high 2 g/day dose was administered, the majority of the subjects (6/8) experienced mild episodic loose stools. Pollack et al. [59] also reported intolerance for higher daily doses of 3 g resveratrol, where three patients suffered severe gastrointestinal symptoms, leading to the hospitalization of one patient. Hence, the dose was reduced to 1 g twice daily, and there were no further complaints of intolerable gastrointestinal side effects. Overall, it appears that the gastrointestinal side effects of resveratrol are dose-dependent. Based on current data, the dose of resveratrol should be limited to 1–2 g/day, but this may compromise its efficacy due to inadequate plasma concentrations achieved at lower doses.

5. Concluding remarks and future perspectives

5.1. Defining the dose and reaching efficacious levels

Currently, it appears that resveratrol is well tolerated at doses of up to 1 g daily, but this dose is unable to generate plasma concentrations equivalent to the effective IC_{50} values for most investigated cancer cells. Yet, higher doses (2–5 g/day) may not be well tolerated and 5 g/day doses may exacerbate certain comorbidities via drug-drug or drug-disease interactions as evidenced in the trial conducted by Popat et al. [56]. Resveratrol tissue levels attained are crucial to achieve anticancer effect; however, few human trials have evaluated tissue levels, and the findings are limited to colonic tissue. Therefore, the distribution of resveratrol in other tissues remains unknown. The high resveratrol levels in colonic tissue suggest that it may be an attractive agent for colorectal cancer treatment. Meanwhile, if such levels are not achievable in other tissues, resveratrol will likely be less useful for other forms of cancer. Obesity-related cancers may be more sensitive to resveratrol, as resveratrol is a lipophilic drug and concentrates in lipophilic compartments. The anticancer efficacy of resveratrol is highly related to the percentage of its major metabolites, and could be improved by synthesizing new derivatives of resveratrol, some of which are shown in Fig. 3.

5.2. How can we enhance bioavailability?

5.2.1. Derivatives of resveratrol for anticancer therapy

Researchers have attempted to elucidate the anticancer effects of resveratrol derivatives, *in vitro* and *in vivo*, relative to parent resveratrol. Pterostilbene (trans-3,5-dimethoxy-4′-hydroxystilbene), has shown greater bioavailability and corresponding plasma levels than parent resveratrol [62], exhibiting 5-fold lower clearance/elimination and 10-fold longer mean transit time than resveratrol. The extra methyl groups of this derivative decrease its vulnerability to conjugation metabolism [63], and its anticancer activity has been shown to exceed that of resveratrol *in vivo* [64]. *Trans*-3,5,4′-trimethoxystilbene induces cell cycle arrest and apoptosis with enhanced potency via a unique mechanism [65,66], and the IC_{50} values were 100–200-fold lower than those of resveratrol. *Trans*-3,4,5,4′-tetramethoxystilbene (DMU212/TMS) has both greater pharmacokinetic and tumour suppressive properties, and its metabolite has displayed higher preclinical cytotoxicity in ovarian [67] and prostate cancer [68]. *Trans*-2,4,3′,4′,5′-pentamethoxystilbene displayed higher potency at inhibiting colon [69] and breast [70] cancer cell growth compared to resveratrol. The hydroxylated analogue piceatannol showed equipotency for anti-inflammatory, immunomodulatory, and anti-proliferative effects, with direct proapoptotic, anti-metastatic [71], and tyrosine-kinase inhibiting activities [72,73]. To date, no cancer-related clinical trials with resveratrol stilbenes have been performed. We identified a single trial on derivative resveratrol-triphosphatase, which showed that the compound elicited greater reduction of oxidative stress in obese subjects [74]; however, little is known about this compound.

5.2.2. Metabolites of resveratrol for anticancer therapy

Many studies [39,44,53,58,61,75] have identified resveratrol-3-O-sulfate as a major metabolite reaching higher plasma and tissue concentrations than resveratrol. Even in diseased individuals, resveratrol-3-O-sulfate levels were approximately 5-fold [58], 10-fold [76] and even 300-fold [77] higher than those of parent resveratrol. Similarly, resveratrol-glucuronides have shown promising plasma concentrations [40,48]. However, efficacy-wise, sulphated metabolites have reported poor cytotoxicity in human breast cancer lines [78], and higher IC_{50} values [79]. Glucuronidated metabolites retained cell growth inhibition activities, but unfortunately demonstrated higher IC_{50} in colon cancer cell lines than resveratrol [80]. Moreover, high levels of resveratrol metabolites did not contribute to an anti-tumour effect in neuroblastoma *in vitro* and *in vivo* [81]. However, Hoshino et al. [82] reported that resveratrol-3-O-sulfate mediates comparable or enhanced antioxidant and anti-inflammatory activities. A modest antiproliferative activity of resveratrol-4′-O-sulfate was also observed in a separate study, and its COX inhibition activity was similar to that of resveratrol [83]. Resveratrol metabolites may not be as valuable as resveratrol for cytotoxicity, but may provide anti-inflammatory and antioxidative effects. The gut metabolite dihydroresveratrol retains some degree of antioxidative and anti-inflammatory activities [84], but may stimulate, rather than inhibit, the proliferation of the ER + breast cancer cell line [85]. Some studies suggest that metabolites have to be deconjugated back to free resveratrol to exert an effect, while other studies suggest that metabolites are not deconjugated but enter and are retained in

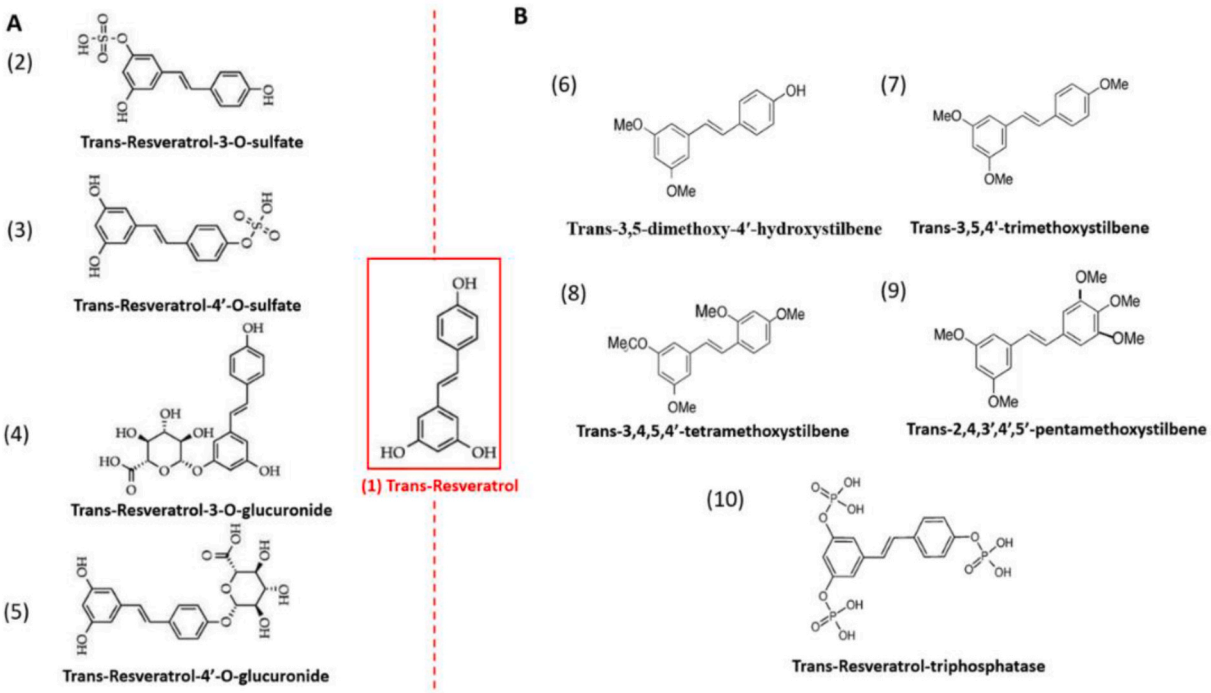

Fig. 3. Chemical structures of resveratrol and its major conjugated metabolites (A), and several derivatives (B). Middle: (1) *Trans*-Resveratrol. (A) Four major conjugated metabolites: (2) *Trans*-Resveratrol-3-O-sulfate, (3) *Trans*-Resveratrol-4′-O-sulfate, (4) *Trans*-Resveratrol-3-O-glucuronide, (5) *Trans*-Resveratrol-4′-O-glucuronide. (B) Derivatives: (6) Trans-3,5-dimethoxy-4′-hydroxystilbene, (7) *Trans*-3,5,4′-trimethoxystilbene, (8) *Trans*-3,4,5,4′-tetramethoxystilbene, (9) *Trans*-2,4,3′,4′,5′-pentamethoxystilbene, (10) *Trans*-Resveratrol-triphosphatase.

tissues, providing long-term tumour-senescent chemoprevention rather short-term biological effects [86]. It is undeniable that the metabolites are present in promising concentrations; however, their biological effects need to be determined.

5.2.3. *Formulations to enhance the bioavailability and efficacy of resveratrol*

More recently, nanotechnology has emerged as a compelling strategy to counter the poor aqueous solubility and bioavailability, which confines the clinical application of resveratrol. Nanoparticle delivery systems such as lipid-core nano-capsules or solid-lipid nanoparticles may be coated on their surface with polyethylene glycol or another inactive moiety such as chitosan, avoiding the reticuloendothelial system and allowing accumulation in tumours through enhanced permeability and retention [36]. Additionally, by incorporating target-specific antigens or ligands on the surface, the drug can reach and be retained at the desired tumour site, offering increased efficacy and reducing undesirable toxicity. Biodegradable nano-formulations also allow for controlled or sustained release systems. The IC_{50} for polymeric nanoparticles encapsulating resveratrol was calculated to be 15.6 μM, which is approximately half the IC_{50} (29.7 μM) of free resveratrol [87]. Phosphonate-modified mesoporous silica nanoparticles displayed augmented antiproliferative activity with a lower IC_{50} of 7.15 μM, as compared to 14.86 μM for free resveratrol [88]. Currently, they are no clinical trials testing nanoparticle formulations and therefore, this should be addressed.

In addition, resveratrol-loaded Ca-pectinate beads and Zn-pectinate microparticles have been developed and repeatedly examined for targeted delivery and sustained release [89–94]. Biodegradable double-layered ultrafine fibres can also provide sustained release [95]. Moreover, complexation with β-cyclodextrins to improve resveratrol solubility has shown favourable outcomes. In addition, the incorporation of resveratrol into liposomes or micelles can combat poor bioavailability [96]. Lastly, clinical trials using micelles [97], galenic soluble formulations [98], or micronized formulations [98] should be carried out.

The recent trials showing dangerous renal toxicity upon treatment with resveratrol highlights that correct patient selection is of paramount importance when developing resveratrol as a potential anticancer agent. At present, despite the exciting results on its efficacy in preclinical models, its low bioavailability due to rapid metabolism prevents it from reaching bioactive plasma concentrations in human subjects, thereby compromising its clinical efficacy. However, the tissue distribution of resveratrol, specifically in the colon, suggests that resveratrol could be an attractive agent for colorectal cancer, while its lipophilic nature may be favourable for obesity-related cancers. Additionally, its unconventional hormetic nature needs further investigation.

In conclusion, we can enhance the bioavailability of resveratrol by developing new formulations. Nano-formulations could be the preferred approach, given their potential capacity to target selective sites and reduce toxicity. It seems reasonable to conduct new trials on resveratrol nano-formulations, or to follow-up and improvise on previously proven novel formulations. Given all the gaps mentioned, much work remains to be done before resveratrol can be considered a therapeutic agent for cancer therapy.

Author contributions

Ren, B.; Kwah, M.X.; and Liu, C. are the lead contributors for this review article through drafting the article; Ma, Z.; Shanmugam, M.K.; Ding, L.; Xiang, X. contributed to acquisition and interpretation of data. Ho, P.C.; Wang, L.; Ong, P.S.; Goh, B.C. contributed to the structure design and to the conception and design of the study as well as to critical revision for important intellectual content.

Declaration of competing interest

The authors declare no conflict of interest.

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References

[1] P. Langcake, R.J. Pryce, The production of resveratrol by Vitis vinifera and other members of the Vitaceae as a response to infection or injury, Physiol. Plant Pathol. 9 (1976) 77–86, https://doi.org/10.1016/0048-4059(76)90077-1.
[2] S. Nonomura, H. Kanagawa, A. Makimoto, Chemical constituents of polygonaceous plants.i.studies on the components of ko.jo.kon. (polygonum cuspidatum sieb.et. zucc), Yakugaku Zasshi 83 (1963) 988–990.
[3] H. Arichi, Y. Kimura, H. Okuda, K. Baba, M. Kozawa, S. Arichi, Effects of stilbene components of the roots of Polygonum cuspidatum Sieb. et Zucc. on lipid metabolism, Chem. Pharm. Bull. (Tokyo) 30 (1982) 1766–1770, https://doi.org/10.1248/cpb.30.1766.
[4] S. Renaud, M. de Lorgeril, Wine, alcohol, platelets, and the French paradox for coronary heart disease, Lancet (London, England) 339 (1992) 1523–1526, https://doi.org/10.1016/0140-6736(92)91277-f.
[5] M.A. Valentovic, Evaluation of resveratrol in cancer patients and experimental models, Adv. Canc. Res. 137 (2018) 171–188, https://doi.org/10.1016/bs.acr.2017.11.006.
[6] M. Jang, L. Cai, G.O. Udeani, K.V. Slowing, C.F. Thomas, C.W. Beecher, H.H. Fong, N.R. Farnsworth, A.D. Kinghorn, R.G. Mehta, et al., Cancer chemopreventive activity of resveratrol, a natural product derived from grapes, Science (New York, N.Y.) 275 (1997) 218–220, https://doi.org/10.1126/science.275.5297.218.
[7] B.B. Aggarwal, A. Bhardwaj, R.S. Aggarwal, N.P. Seeram, S. Shishodia, Y. Takada, Role of resveratrol in prevention and therapy of cancer: preclinical and clinical studies, Anticancer Res. 24 (2004) 2783–2840.
[8] J. Burns, T. Yokota, H. Ashihara, M.E.J. Lean, A. Crozier, Plant foods and herbal sources of resveratrol, J. Agric. Food Chem. 50 (2002) 3337–3340, https://doi.org/10.1021/jf0112973.
[9] W.J. Hurst, J.A. Glinski, K.B. Miller, J. Apgar, M.H. Davey, D.A. Stuart, Survey of the trans-resveratrol and trans-piceid content of cocoa-containing and chocolate products, J. Agric. Food Chem. 56 (2008) 8374–8378, https://doi.org/10.1021/jf801297w.
[10] M.A. Vian, V. Tomao, S. Gallet, P.O. Coulomb, J.M. Lacombe, Simple and rapid method for cis- and trans-resveratrol and piceid isomers determination in wine by high-performance liquid chromatography using chromolith columns, J. Chromatogr. A 1085 (2005) 224–229, https://doi.org/10.1016/j.chroma.2005.05.083.
[11] Š. Zupančič, Z. Lavrič, J. Kristl, Stability and solubility of trans-resveratrol are strongly influenced by pH and temperature, Eur. J. Pharm. Biopharm. 93 (2015) 196–204, https://doi.org/10.1016/j.ejpb.2015.04.002.
[12] S. Fulda, Resveratrol and derivatives for the prevention and treatment of cancer, Drug Discov. Today 15 (2010) 757–765, https://doi.org/10.1016/j.drudis.2010.07.005.
[13] A. Wahab, K. Gao, C. Jia, F. Zhang, G. Tian, G. Murtaza, J. Chen, Significance of resveratrol in clinical management of chronic diseases, Molecules 22 (2017), https://doi.org/10.3390/molecules22081329.
[14] J.-H. Ko, G. Sethi, J.-Y. Um, M.K. Shanmugam, F. Arfuso, A.P. Kumar, A. Bishayee, K.S. Ahn, The role of resveratrol in cancer therapy, Int. J. Mol. Sci. 18 (2017) 2589, https://doi.org/10.3390/ijms18122589.
[15] S.H. Baek, J.-H. Ko, H. Lee, J. Jung, M. Kong, J.-w. Lee, J. Lee, A. Chinnathambi, M. E. Zayed, S.A. Alharbi, et al., Resveratrol inhibits STAT3 signaling pathway through the induction of SOCS-1: role in apoptosis induction and radiosensitization in head and neck tumor cells, Phytomedicine 23 (2016) 566–577, https://doi.org/10.1016/j.phymed.2016.02.011.
[16] K.B. Harikumar, A.B. Kunnumakkara, G. Sethi, P. Diagaradjane, P. Anand, M. K. Pandey, J. Gelovani, S. Krishnan, S. Guha, B.B. Aggarwal, Resveratrol, a multitargeted agent, can enhance antitumor activity of gemcitabine in vitro and in orthotopic mouse model of human pancreatic cancer, Int. J. Canc. 127 (2010) 257–268, https://doi.org/10.1002/ijc.25041.
[17] L.G. Carter, J.A. D'Orazio, K.J. Pearson, Resveratrol and cancer: focus on in vivo evidence, Endocr. Relat. Canc. 21 (2014) R209–R225, https://doi.org/10.1530/erc-13-0171.
[18] M. Yousef, I.A. Vlachogiannis, E. Tsiani, Effects of resveratrol against lung cancer: in vitro and in vivo studies, Nutrients 9 (2017) 1231, https://doi.org/10.3390/nu9111231.
[19] V.M. Adhami, F. Afaq, N. Ahmad, Suppression of ultraviolet B exposure-mediated activation of NF-kappaB in normal human keratinocytes by resveratrol, Neoplasia 5 (2003) 74–82, https://doi.org/10.1016/s1476-5586(03)80019-2.
[20] J.L. Espinoza, Y. Kurokawa, A. Takami, Rationale for assessing the therapeutic potential of resveratrol in hematological malignancies, Blood Rev. 33 (2019) 43–52, https://doi.org/10.1016/j.blre.2018.07.001.
[21] M. Ashrafizadeh, Z. Ahmadi, T. Farkhondeh, S. Samarghandian, Resveratrol targeting the Wnt signaling pathway: a focus on therapeutic activities, J. Cell. Physiol. 235 (2020) 4135–4145, https://doi.org/10.1002/jcp.29327.
[22] Q. Ji, X. Liu, X. Fu, L. Zhang, H. Sui, L. Zhou, J. Sun, J. Cai, J. Qin, J. Ren, et al., Resveratrol inhibits invasion and metastasis of colorectal cancer cells via MALAT1 mediated Wnt/β-catenin signal pathway, PloS One 8 (2013), e78700, https://doi.org/10.1371/journal.pone.0078700.
[23] Q. Ji, X. Liu, Z. Han, L. Zhou, H. Sui, L. Yan, H. Jiang, J. Ren, J. Cai, Q. Li, Resveratrol suppresses epithelial-to-mesenchymal transition in colorectal cancer through TGF-β1/Smads signaling pathway mediated Snail/E-cadherin expression, BMC Canc. 15 (2015) 97, https://doi.org/10.1186/s12885-015-1119-y.
[24] C. Buhrmann, M. Yazdi, B. Popper, P. Shayan, A. Goel, B.B. Aggarwal, M. Shakibaei, Evidence that TNF-β induces proliferation in colorectal cancer cells and resveratrol can down-modulate it, Exp. Biol. Med. 244 (2019) 1–12, https://doi.org/10.1177/1535370218824538.
[25] J.L. Su, C.Y. Yang, M. Zhao, M.L. Kuo, M.L. Yen, Forkhead proteins are critical for bone morphogenetic protein-2 regulation and anti-tumor activity of resveratrol, J. Biol. Chem. 282 (2007) 19385–19398, https://doi.org/10.1074/jbc.M702452200.
[26] A. Kotha, M. Sekharam, L. Cilenti, K. Siddiquee, A. Khaled, A.S. Zervos, B. Carter, J. Turkson, R. Jove, Resveratrol inhibits Src and Stat3 signaling and induces the apoptosis of malignant cells containing activated Stat3 protein, Mol. Canc. Therapeut. 5 (2006) 621–629, https://doi.org/10.1158/1535-7163.Mct-05-0268.
[27] Z. Cao, J. Fang, C. Xia, X. Shi, B.H. Jiang, trans-3,4,5'-Trihydroxystibene inhibits hypoxia-inducible factor 1alpha and vascular endothelial growth factor expression in human ovarian cancer cells, Clin. Canc. Res. 10 (2004) 5253–5263, https://doi.org/10.1158/1078-0432.Ccr-03-0588.
[28] J.M. Pezzuto, The phenomenon of resveratrol: redefining the virtues of promiscuity, Ann. N. Y. Acad. Sci. 1215 (2011) 123–130, https://doi.org/10.1111/j.1749-6632.2010.05849.x.
[29] 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. 240 (2015) 1672–1681, https://doi.org/10.1177/1535370215573396.
[30] M. Fukui, N. Yamabe, K.S. Kang, B.T. Zhu, Growth-stimulatory effect of resveratrol in human cancer cells, Mol. Carcinog. 49 (2010) 750–759, https://doi.org/10.1002/mc.20650.
[31] S. Fulda, K.-M. Debatin, Sensitization for anticancer drug-induced apoptosis by the chemopreventive agent resveratrol, Oncogene 23 (2004) 6702–6711, https://doi.org/10.1038/sj.onc.1207630.
[32] D. Ivanova, Z. Zhelev, S. Semkova, I. Aoki, R. Bakalova, Resveratrol modulates the redox-status and cytotoxicity of anticancer drugs by sensitizing leukemic lymphocytes and protecting normal lymphocytes, Anticancer Res. 39 (2019) 3745–3755, https://doi.org/10.21873/anticanres.13523.
[33] I. Leon-Galicia, J. Diaz-Chavez, M.E. Albino-Sanchez, E. Garcia-Villa, R. Bermudez-Cruz, J. Garcia-Mena, L.A. Herrera, A. García-Carrancá, P. Gariglio, Resveratrol decreases Rad51 expression and sensitizes cisplatin-resistant MCF-7 breast cancer cells, Oncol. Rep. 39 (2018) 3025–3033, https://doi.org/10.3892/or.2018.6336.
[34] L.H. Engelke, A. Hamacher, P. Proksch, M.U. Kassack, Ellagic acid and resveratrol prevent the development of cisplatin resistance in the epithelial ovarian cancer cell line A2780, J. Canc. 7 (2016) 353–363, https://doi.org/10.7150/jca.13754.
[35] G. Şimşek, S. Gürocak, N. Karadağ, A.B. Karabulut, E. Demirtaş, E. Karataş, E. Pepele, Protective effects of resveratrol on salivary gland damage induced by total body irradiation in rats, Laryngoscope 122 (2012) 2743–2748, https://doi.org/10.1002/lary.23609.
[36] I.A. Siddiqui, V. Sanna, N. Ahmad, M. Sechi, H. Mukhtar, Resveratrol nanoformulation for cancer prevention and therapy, Ann. N. Y. Acad. Sci. 1348 (2015) 20–31, https://doi.org/10.1111/nyas.12811.
[37] D.J. Boocock, G.E.S. Faust, K.R. Patel, A.M. Schinas, V.A. Brown, M.P. Ducharme, T.D. Booth, J.A. Crowell, M. Perloff, A.J. Gescher, et al., Phase I dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemopreventive agent, Cancer Epidemiol. Biomark. Prev. 16 (2007) 1246–1252, https://doi.org/10.1158/1055-9965.EPI-07-0022.
[38] N.s.-K. Cn, C. St-Louis, M. Beauregard, M. Subirade, R. Carpentier, S. Hotchandani, H.A. Tajmir-Riahi, Resveratrol binding to human serum albumin, J. Biomol. Struct. Dyn. 24 (2006) 277–283, https://doi.org/10.1080/07391102.2006.10507120.
[39] V.A. Brown, K.R. Patel, M. Viskaduraki, J.A. Crowell, M. Perloff, T.D. Booth, G. Vasilinin, A. Sen, A.M. Schinas, G. Piccirilli, et al., Repeat dose study of the cancer chemopreventive agent resveratrol in healthy volunteers: safety, pharmacokinetics, and effect on the insulin-like growth factor axis, Canc. Res. 70 (2010) 9003–9011, https://doi.org/10.1158/0008-5472.CAN-10-2364.
[40] W. Zhu, W. Qin, K. Zhang, G.E. Rottinghaus, Y.C. Chen, B. Kliethermes, E.R. Sauter, Trans-resveratrol alters mammary promoter hypermethylation in women at increased risk for breast cancer, Nutr. Canc. 64 (2012) 393–400, https://doi.org/10.1080/01635581.2012.654926.
[41] J.L. Espinoza, L.Q. Trung, P.T. Inaoka, K. Yamada, D.T. An, S. Mizuno, S. Nakao, A. Takami, The repeated administration of resveratrol has measurable effects on circulating T-cell subsets in humans, Oxid. Med. Cell. Longev. 2017 (2017), https://doi.org/10.1155/2017/6781872, 6781872-6781872.
[42] R.F. Holcombe, M. Martinez, K. Planutis, M. Planutiene, Effects of a grape-supplemented diet on proliferation and Wnt signaling in the colonic mucosa are greatest for those over age 50 and with high arginine consumption, Nutr. J. 14 (2015), https://doi.org/10.1186/s12937-015-0050-z, 62-62.
[43] A.V. Nguyen, M. Martinez, M.J. Stamos, M.P. Moyer, K. Planutis, C. Hope, R. F. Holcombe, Results of a phase I pilot clinical trial examining the effect of plant-derived resveratrol and grape powder on Wnt pathway target gene expression in colonic mucosa and colon cancer, Canc. Manag. Res. 1 (2009) 25–37.
[44] H.H.S. Chow, L.L. Garland, C.-H. Hsu, D.R. Vining, W.M. Chew, J.A. Miller, M. Perloff, J.A. Crowell, D.S. Alberts, Resveratrol modulates drug- and carcinogen-

metabolizing enzymes in a healthy volunteer study, Canc. Prev. Res. 3 (2010) 1168–1175, https://doi.org/10.1158/1940-6207.CAPR-09-0155.
[45] L.M. Howells, D.P. Berry, P.J. Elliott, E.W. Jacobson, E. Hoffmann, B. Hegarty, K. Brown, W.P. Steward, A.J. Gescher, Phase I randomized, double-blind pilot study of micronized resveratrol (SRT501) in patients with hepatic metastases–safety, pharmacokinetics, and pharmacodynamics, Canc. Prev. Res. 4 (2011) 1419–1425, https://doi.org/10.1158/1940-6207.CAPR-11-0148.
[46] H. Cai, E. Scott, A. Kholghi, C. Andreadi, A. Rufini, A. Karmokar, R.G. Britton, E. Horner-Glister, P. Greaves, D. Jawad, et al., Cancer chemoprevention: evidence of a nonlinear dose response for the protective effects of resveratrol in humans and mice, Sci. Transl. Med. 7 (2015), https://doi.org/10.1126/scitranslmed.aaa7619, 298ra117-298ra117.
[47] K.R. Patel, V.A. Brown, D.J. Jones, R.G. Britton, D. Hemingway, A.S. Miller, K. P. West, T.D. Booth, M. Perloff, J.A. Crowell, et al., Clinical pharmacology of resveratrol and its metabolites in colorectal cancer patients, Canc. Res. 70 (2010) 7392–7399, https://doi.org/10.1158/0008-5472.Can-10-2027.
[48] M.Á. Ávila-Gálvez, R. García-Villalba, F. Martínez-Díaz, B. Ocaña-Castillo, T. Monedero-Saiz, A. Torrecillas-Sánchez, B. Abellán, A. González-Sarrías, J. C. Espín, Metabolic profiling of dietary polyphenols and methylxanthines in normal and malignant mammary tissues from breast cancer patients, Mol. Nutr. Food Res. 63 (2019), https://doi.org/10.1002/mnfr.201801239 e1801239-e1801239.
[49] C.J. Paller, M.A. Rudek, X.C. Zhou, W.D. Wagner, T.S. Hudson, N. Anders, H. J. Hammers, D. Dowling, S. King, E.S. Antonarakis, et al., A phase I study of muscadine grape skin extract in men with biochemically recurrent prostate cancer: safety, tolerability, and dose determination, Prostate 75 (2015) 1518–1525, https://doi.org/10.1002/pros.23024.
[50] C.J. Paller, X.C. Zhou, E.I. Heath, M.-E. Taplin, T. Mayer, M.N. Stein, G.J. Bubley, R. Pili, T. Hudson, R. Kakarla, et al., Muscadine grape skin extract (MPX) in men with biochemically recurrent prostate cancer: a randomized, multicenter, placebo-controlled clinical trial, Clin. Canc. Res. 24 (2018) 306–315, https://doi.org/10.1158/1078-0432.CCR-17-1100.
[51] M.D. van Die, S.G. Williams, J. Emery, K.M. Bone, J.M.G. Taylor, E. Lusk, M. V. Pirotta, A placebo-controlled double-blinded randomized pilot study of combination phytotherapy in biochemically recurrent prostate cancer, Prostate 77 (2017) 765–775, https://doi.org/10.1002/pros.23317.
[52] C. la Porte, N. Voduc, G. Zhang, I. Seguin, D. Tardiff, N. Singhal, D.W. Cameron, Steady-State pharmacokinetics and tolerability of trans-resveratrol 2000 mg twice daily with food, quercetin and alcohol (ethanol) in healthy human subjects, Clin. Pharmacokinet. 49 (2010) 449–454, https://doi.org/10.2165/11531820-000000000-00000.
[53] H.H.S. Chow, L.L. Garland, B.M. Heckman-Stoddard, C.-H. Hsu, V.D. Butler, C. A. Cordova, W.M. Chew, T.L. Cornelison, A pilot clinical study of resveratrol in postmenopausal women with high body mass index: effects on systemic sex steroid hormones, J. Transl. Med. 12 (2014), https://doi.org/10.1186/s12967-014-0223-0, 223-223.
[54] J.P. Crandall, V. Oram, G. Trandafirescu, M. Reid, P. Kishore, M. Hawkins, H. W. Cohen, N. Barzilai, Pilot study of resveratrol in older adults with impaired glucose tolerance, J. Gerontol. A Biol. Sci. Med. Sci. 67 (2012) 1307–1312, https://doi.org/10.1093/gerona/glr235.
[55] A. Movahed, I. Nabipour, X. Lieben Louis, S.J. Thandapilly, L. Yu, M. Kalantarhormozi, S.J. Rekabpour, T. Netticadan, Antihyperglycemic effects of short term resveratrol supplementation in type 2 diabetic patients, Evid. Based Complement. Alternat. Med. 2013 (2013) 851267, https://doi.org/10.1155/2013/851267.
[56] R. Popat, T. Plesner, F. Davies, G. Cook, M. Cook, P. Elliott, E. Jacobson, T. Gumbleton, H. Oakervee, J. Cavenagh, A phase 2 study of SRT501 (resveratrol) with bortezomib for patients with relapsed and or refractory multiple myeloma, Br. J. Haematol. 160 (2013) 714–717, https://doi.org/10.1111/bjh.12154.
[57] N. Grzasko, M. Morawska, M. Hus, Optimizing the treatment of patients with multiple myeloma and renal impairment, Clin. Lymphoma, Myeloma & Leukemia 15 (2015) 187–198, https://doi.org/10.1016/j.clml.2014.09.012.
[58] E.M. Yiu, G. Tai, R.E. Peverill, K.J. Lee, K.D. Croft, T.A. Mori, B. Scheiber-Mojdehkar, B. Sturm, M. Praschberger, A.P. Vogel, et al., An open-label trial in Friedreich ataxia suggests clinical benefit with high-dose resveratrol, without effect on frataxin levels, J. Neurol. 262 (2015) 1344–1353, https://doi.org/10.1007/s00415-015-7719-2.
[59] C. la Porte, N. Voduc, G. Zhang, I. Seguin, D. Tardiff, N. Singhal, D.W. Cameron, Steady-State pharmacokinetics and tolerability of trans-resveratrol 2000 mg twice daily with food, quercetin and alcohol (ethanol) in healthy human subjects, Clin. Pharmacokinet. 49 (2010) 449–454, https://doi.org/10.2165/11531820-000000000-00000.
[60] H.H. Chow, L.L. Garland, C.H. Hsu, D.R. Vining, W.M. Chew, J.A. Miller, M. Perloff, J.A. Crowell, D.S. Alberts, Resveratrol modulates drug- and carcinogen-metabolizing enzymes in a healthy volunteer study, Canc. Prev. Res. 3 (2010) 1168–1175, https://doi.org/10.1158/1940-6207.Capr-09-0155.
[61] K.R. Patel, V.A. Brown, D.J.L. Jones, R.G. Britton, D. Hemingway, A.S. Miller, K. P. West, T.D. Booth, M. Perloff, J.A. Crowell, et al., Clinical pharmacology of resveratrol and its metabolites in colorectal cancer patients, Canc. Res. 70 (2010) 7392–7399, https://doi.org/10.1158/0008-5472.CAN-10-2027.
[62] I.M. Kapetanovic, M. Muzzio, Z. Huang, T.N. Thompson, D.L. McCormick, Pharmacokinetics, oral bioavailability, and metabolic profile of resveratrol and its dimethylether analog, pterostilbene, in rats, Canc. Chemother. Pharmacol. 68 (2011) 593–601, https://doi.org/10.1007/s00280-010-1525-4.
[63] S.C.M. Yeo, P.C. Ho, H.-S. Lin, Pharmacokinetics of pterostilbene in Sprague-Dawley rats: the impacts of aqueous solubility, fasting, dose escalation, and dosing route on bioavailability, Mol. Nutr. Food Res. 57 (2013) 1015–1025, https://doi.org/10.1002/mnfr.201200651.
[64] S. Fulda, Resveratrol and derivatives for the prevention and treatment of cancer, Drug Discov. Today 15 (2010) 757–765, https://doi.org/10.1016/j.drudis.2010.07.005.
[65] M.-C. Scherzberg, A. Kiehl, A. Zivkovic, H. Stark, J. Stein, R. Fürst, D. Steinhilber, S. Ulrich-Rückert, Structural modification of resveratrol leads to increased anti-tumor activity, but causes profound changes in the mode of action, Toxicol. Appl. Pharmacol. 287 (2015) 67–76, https://doi.org/10.1016/j.taap.2015.05.020.
[66] F.S. Aldawsari, C.A. Velázquez-Martínez, 3,4',5-trans-Trimethoxystilbene; a natural analogue of resveratrol with enhanced anticancer potency, Invest. N. Drugs 33 (2015) 775–786, https://doi.org/10.1007/s10637-015-0222-x.
[67] H. Piotrowska-Kempisty, M. Ruciński, S. Borys, M. Kucińska, M. Kaczmarek, P. Zawierucha, M. Wierzchowski, D. Łażewski, M. Murias, J. Jodynis-Liebert, 3'-hydroxy-3,4,5,4'-tetramethoxystilbene, the metabolite of resveratrol analogue DMU-212, inhibits ovarian cancer cell growth in vitro and in a mice xenograft model, Sci. Rep. 6 (2016) 32627, https://doi.org/10.1038/srep32627.
[68] Z. Horvath, S. Marihart-Fazekas, P. Saiko, M. Grusch, M. Ozsüy, M. Harik, N. Handler, T. Erker, W. Jaeger, M. Fritzer-Szekeres, et al., Novel resveratrol derivatives induce apoptosis and cause cell cycle arrest in prostate cancer cell lines, Anticancer Res. 27 (2007) 3459–3464.
[69] H. Li, W.K. Wu, Z. Zheng, C.T. Che, L. Yu, Z.J. Li, Y.C. Wu, K.W. Cheng, J. Yu, C. H. Cho, et al., 2,3',4,4',5'-Pentamethoxy-trans-stilbene, a resveratrol derivative, is a potent inducer of apoptosis in colon cancer cells via targeting microtubules, Biochem. Pharmacol. 78 (2009) 1224–1232, https://doi.org/10.1016/j.bcp.2009.06.109.
[70] M.H. Pan, C.L. Lin, J.H. Tsai, C.T. Ho, W.J. Chen, 3,5,3',4',5'-pentamethoxystilbene (MR-5), a synthetically methoxylated analogue of resveratrol, inhibits growth and induces G1 cell cycle arrest of human breast carcinoma MCF-7 cells, J. Agric. Food Chem. 58 (2010) 226–234, https://doi.org/10.1021/jf903067g.
[71] M.A. Seyed, I. Jantan, S.N.A. Bukhari, K. Vijayaraghavan, A comprehensive review on the chemotherapeutic potential of piceatannol for cancer treatment, with mechanistic insights, J. Agric. Food Chem. 64 (2016) 725–737, https://doi.org/10.1021/acs.jafc.5b05993.
[72] R.L. Geahlen, J.L. McLaughlin, Piceatannol (3,4,3',5'-tetrahydroxy-trans-stilbene) is a naturally occurring protein-tyrosine kinase inhibitor, Biochem. Biophys. Res. Commun. 165 (1989) 241–245, https://doi.org/10.1016/0006-291x(89)91060-7.
[73] K.H. Choi, J.E. Kim, N.R. Song, J.E. Son, M.K. Hwang, S. Byun, J.H. Kim, K.W. Lee, H.J. Lee, Phosphoinositide 3-kinase is a novel target of piceatannol for inhibiting PDGF-BB-induced proliferation and migration in human aortic smooth muscle cells, Cardiovasc. Res. 85 (2010) 836–844, https://doi.org/10.1093/cvr/cvp359.
[74] D. De Groote, K. Van Belleghem, J. Devière, W. Van Brussel, A. Mukaneza, L. Amininejad, Effect of the intake of resveratrol, resveratrol phosphate, and catechin-rich grape seed extract on markers of oxidative stress and gene expression in adult obese subjects, Ann. Nutr. Metab. 61 (2012) 15–24, https://doi.org/10.1159/000338634.
[75] V.B. Patel, S. Misra, B.B. Patel, A.P.N. Majumdar, Colorectal cancer: chemopreventive role of curcumin and resveratrol, Nutr. Canc. 62 (2010) 958–967, https://doi.org/10.1080/01635581.2010.510259.
[76] C. Vors, C. Couillard, M.-E. Paradis, I. Gigleux, J. Marin, M.-C. Vohl, P. Couture, B. Lamarche, Supplementation with resveratrol and curcumin does not affect the inflammatory response to a high-fat meal in older adults with abdominal obesity: a randomized, placebo-controlled crossover trial, J. Nutr. 148 (2018) 379–388, https://doi.org/10.1093/jn/nxx072.
[77] R.S. Turner, R.G. Thomas, S. Craft, C.H. van Dyck, J. Mintzer, B.A. Reynolds, J. B. Brewer, R.A. Rissman, R. Raman, P.S. Aisen, et al., A randomized, double-blind, placebo-controlled trial of resveratrol for Alzheimer disease, Neurology 85 (2015) 1383–1391, https://doi.org/10.1212/WNL.0000000000002035.
[78] M. Miksits, K. Wlcek, M. Svoboda, O. Kunert, E. Haslinger, T. Thalhammer, T. Szekeres, W. Jäger, Antitumor activity of resveratrol and its sulfated metabolites against human breast cancer cells, Planta Med. 75 (2009) 1227–1230, https://doi.org/10.1055/s-0029-1185533.
[79] M. Murias, M. Miksits, S. Aust, M. Spatzenegger, T. Thalhammer, T. Szekeres, W. Jaeger, Metabolism of resveratrol in breast cancer cell lines: impact of sulfotransferase 1A1 expression on cell growth inhibition, Canc. Lett. 261 (2008) 172–182, https://doi.org/10.1016/j.canlet.2007.11.008.
[80] E. Polycarpou, L.B. Meira, S. Carrington, E. Tyrrell, H. Modjtahedi, M.A. Carew, Resveratrol 3-O-D-glucuronide and resveratrol 4'-O-D-glucuronide inhibit colon cancer cell growth: evidence for a role of A3 adenosine receptors, cyclin D1 depletion, and G1 cell cycle arrest, Mol. Nutr. Food Res. 57 (2013) 1708–1717, https://doi.org/10.1002/mnfr.201200742.
[81] J.D. Kenealey, L. Subramanian, P.R. Van Ginkel, S. Darjatmoko, M.J. Lindstrom, V. Somoza, S.K. Ghosh, Z. Song, R.P. Hsung, G.S. Kwon, et al., Resveratrol metabolites do not elicit early pro-apoptotic mechanisms in neuroblastoma cells, J. Agric. Food Chem. 59 (2011) 4979–4986, https://doi.org/10.1021/jf104901g.
[82] J. Hoshino, E.-J. Park, T.P. Kondratyuk, L. Marler, J.M. Pezzuto, R.B. van Breemen, S. Mo, Y. Li, M. Cushman, Selective synthesis and biological evaluation of sulfate-conjugated resveratrol metabolites, J. Med. Chem. 53 (2010) 5033–5043, https://doi.org/10.1021/jm100274c.
[83] B. Calamini, K. Ratia, M.G. Malkowski, M. Cuendet, J.M. Pezzuto, B.D. Santarsiero, A.D. Mesecar, Pleiotropic mechanisms facilitated by resveratrol and its metabolites, Biochem. J. 429 (2010) 273–282, https://doi.org/10.1042/bj20091857.
[84] D.L. Lu, D.J. Ding, W.J. Yan, R.R. Li, F. Dai, Q. Wang, S.S. Yu, Y. Li, X.L. Jin, B. Zhou, Influence of glucuronidation and reduction modifications of resveratrol on

its biological activities, Chembiochem 14 (2013) 1094–1104, https://doi.org/10.1002/cbic.201300080.
[85] A.A. Gakh, N.Y. Anisimova, M.V. Kiselevsky, S.V. Sadovnikov, I.N. Stankov, M. V. Yudin, K.A. Rufanov, M.Y. Krasavin, A.V. Sosnov, Dihydro-resveratrol—a potent dietary polyphenol, Bioorg. Med. Chem. Lett 20 (2010) 6149–6151, https://doi.org/10.1016/j.bmcl.2010.08.002.
[86] J.A. Giménez-Bastida, M. Ávila-Gálvez, J.C. Espín, A. González-Sarrías, Conjugated physiological resveratrol metabolites induce senescence in breast cancer cells: role of p53/p21 and p16/Rb pathways, and ABC transporters, Mol. Nutr. Food Res. 63 (2019), e1900629, https://doi.org/10.1002/mnfr.201900629.
[87] A.M. Nassir, N. Shahzad, I.A.A. Ibrahim, I. Ahmad, S. Md, M.R. Ain, Resveratrol-loaded PLGA nanoparticles mediated programmed cell death in prostate cancer cells, Saudi Pharmaceut. J. 26 (2018) 876–885, https://doi.org/10.1016/j.jsps.2018.03.009.
[88] Z. Chaudhary, S. Subramaniam, G.M. Khan, M.M. Abeer, Z. Qu, T. Janjua, T. Kumeria, J. Batra, A. Popat, Encapsulation and controlled release of resveratrol within functionalized mesoporous silica nanoparticles for prostate cancer therapy, Front Bioeng Biotechnol 7 (2019) 225, https://doi.org/10.3389/fbioe.2019.00225.
[89] S. Das, K.Y. Ng, P.C. Ho, Formulation and optimization of zinc-pectinate beads for the controlled delivery of resveratrol, AAPS PharmSciTech 11 (2010) 729–742, https://doi.org/10.1208/s12249-010-9435-7.
[90] S. Das, K.Y. Ng, Colon-specific delivery of resveratrol: optimization of multi-particulate calcium-pectinate carrier, Int. J. Pharm. 385 (2010) 20–28, https://doi.org/10.1016/j.ijpharm.2009.10.016.
[91] S. Das, K.Y. Ng, Resveratrol-loaded calcium-pectinate beads: effects of formulation parameters on drug release and bead characteristics, J. Pharm. Sci. 99 (2010) 840–860, https://doi.org/10.1002/jps.21880.
[92] S. Das, A. Chaudhury, K.Y. Ng, Preparation and evaluation of zinc-pectin-chitosan composite particles for drug delivery to the colon: role of chitosan in modifying in vitro and in vivo drug release, Int. J. Pharm. 406 (2011) 11–20, https://doi.org/10.1016/j.ijpharm.2010.12.015.
[93] S. Das, A. Chaudhury, K.Y. Ng, Polyethyleneimine-modified pectin beads for colon-specific drug delivery: in vitro and in vivo implications, J. Microencapsul. 28 (2011) 268–279, https://doi.org/10.3109/02652048.2011.559284.
[94] S. Das, K.Y. Ng, P.C. Ho, Design of a pectin-based microparticle formulation using zinc ions as the cross-linking agent and glutaraldehyde as the hardening agent for colonic-specific delivery of resveratrol: in vitro and in vivo evaluations, J. Drug Target. 19 (2011) 446–457, https://doi.org/10.3109/1061186x.2010.504272.
[95] Z.M. Huang, C.L. He, A. Yang, Y. Zhang, X.J. Han, J. Yin, Q. Wu, Encapsulating drugs in biodegradable ultrafine fibers through co-axial electrospinning, J. Biomed. Mater. Res. 77 (2006) 169–179, https://doi.org/10.1002/jbm.a.30564.
[96] A. Amri, J.C. Chaumeil, S. Sfar, C. Charrueau, Administration of resveratrol: what formulation solutions to bioavailability limitations? J. Contr. Release 158 (2012) 182–193, https://doi.org/10.1016/j.jconrel.2011.09.083.
[97] L.A. Calvo-Castro, C. Schiborr, F. David, H. Ehrt, J. Voggel, N. Sus, D. Behnam, A. Bosy-Westphal, J. Frank, The oral bioavailability of trans-resveratrol from a grapevine-shoot extract in healthy humans is significantly increased by micellar solubilization, Mol. Nutr. Food Res. 62 (2018) 1701057, https://doi.org/10.1002/mnfr.201701057.
[98] M.J. Amiot, B. Romier, T.-M. Anh Dao, R. Fanciullino, J. Ciccolini, R. Burcelin, L. Pechere, C. Emond, J.-F. Savouret, E. Seree, Optimization of trans-Resveratrol bioavailability for human therapy, Biochimie 95 (2013) 1233–1238, https://doi.org/10.1016/j.biochi.2013.01.008.