

Resveratrol as a potential broad-spectrum compound for cancer treatment

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Abstract: There is a need to shift the paradigm of cancer therapeutic approach. The severe adverse side effects, drug resistance and unaffordable price plagued with chemotherapeutic drugs has spurred the development of “dirty drug”. Natural products, specifically phytochemicals, have gained much attention due to their ability to target multiple interconnected pathways. Resveratrol (RSV), the stilbenes found in red wine, is one of the phytochemicals that exhibits various pharmacological therapeutic effects including cancer. In this review, we highlighted RSV as a potential “broad-spectrum” anticancer compound, by summarising its targeting mechanisms in the pathways relevant to the cancer hallmarks.

Keywords: stilbene; hallmarks; dirty drug; natural product; metabolites

Received: 8th June 2020

Accepted: 8th July 2020

Published Online: 18th July 2020

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Citation: Tan LKS, How CW, Foo JB, *et al.* Resveratrol as a potential broad-spectrum compound for Cancer treatment. *Prog Microbes Mol Biol* 2020; 3(1): a0000098. <https://doi.org/10.3687/pmmb.a0000098>.

INTRODUCTION

Cancer, the most commonly diagnosed non-communicable disease, has imparted significant mortality and morbidity worldwide^[1]. In 2018, the World Health Organisation ranked cancers as the leading cause of premature death with 9.6 million cases reported worldwide^[2]. Despite the advancement in cancer therapy, the overall survival rate and quality of life of cancer patients have not been improved. The development of personalised drug on the other hand, is slow, costly and may not guarantee good clinical outcomes. Particular attention has been devoted to explore the potential of pleiotropic, “broad-spectrum” compounds or “dirty drugs” which could simultaneously target multiple mechanisms to overcome the aforementioned issues in achieving effective cancer treatment^[3].

The ten cancer hallmarks proposed by Hanahan and Weinberg in 2011, has become a general a guide to evaluate the potential of specific compound as a promising “dirty drug”^[4]. This means compounds that could disrupt any of the processes responsible for the cancer hallmarks

would almost certainly hinder cancer progression. In an ideal circumstance, a compound that could disrupt multiple pathways not only would produce superior effect, it would also minimise the risk of side effects that is otherwise introduced by multiple drug administration. Natural products have been a rich and excellent source to search for multi-target bioactive compounds with improved therapeutic efficacy and safety^[5,6]. These multi-target bioactive compounds are derived from natural sources such as plants^[7,8], microorganisms^[9-16] and animals^[17]. In a work published by Block *et al.* (2015)^[3], they found that most of the compounds that targets all cancer hallmarks were the phytochemicals. Phytochemicals are naturally produced as a result of evolution against pathogens with evident role playing in human health. These natural compounds have attracted much attention from community for their promising effects in treating diseases^[18-22]. Stilbenes are one of the examples of secondary metabolites that was produced in stressful condition to fight against fungal infection and UV radiation^[23]. It is one of the nonflavonoids which consists of two aromatic rings linked by an ethylene

or ethane bridge (C6-C2-C6 carbon skeleton) and usually found in plants. Among the 400 natural stilbenes discovered, RSV is the most widely investigated compound due to its vast pharmacological activities^[24].

RESVERATROL

Resveratrol (3,4',5-trihydroxy-trans-stilbene) (RSV) (**Figure 1**) can be found in the skin of grapes, red wines, peanuts, pineapple and mulberries. This compound could be synthesised from phenylalanine pathway through several enzyme reactions into para-coumaroyl-CoA, which is condensed with malonyl CoA to form RSV^[25]. Since the discovery of RSV by Siemann and Creasy in red wine in 1992^[26], extensive studies have proven that RSV exhibits its biological functions such as antimicrobial, cardiovascular disease, anticancer, anti-inflammatory, antidiabetic and neurodegenerative diseases^[27,28]. It is believed that most of the pharmacological activities are attributed to its anti-oxidant mechanisms involving the competition with coenzyme Q, free radical scavenging and inhibition of lipid peroxidase in the mitochondria^[29].

RSV has demonstrated anti-cancer properties in both

in vitro and *in vivo* settings. The type of cancers tested are ovarian^[30], lung^[31], colon^[32], prostate^[33], breast^[34] and cervical cancers^[35]. As a pleiotropic compound which acts on different mechanisms, it also showed to play a possible role to counteract multidrug resistance^[36]. As of June 2020, the keywords of “resveratrol and cancer” brings up 3660 results in PubMed database. Correspondingly, RSV possesses great commercial value as evidence by a surge in patent filed in *The Lens* patent database (<http://lens.org>) related to the application of RSV in cancer therapy in recent decades (**Figure 2**).

MODULATION OF CANCER HALLMARKS

The surge of publications and patents undeniable reflect the increased interest of the scientific community toward the therapeutic effect of RSV. In an attempt to investigate the potential of RSV as a “broad spectrum” chemotherapeutic agent, this review summarised the cancer hallmarks and the target molecules that have been claimed to be modulated by RSV in various cancer cell lines and animal models (**Figure 3**).

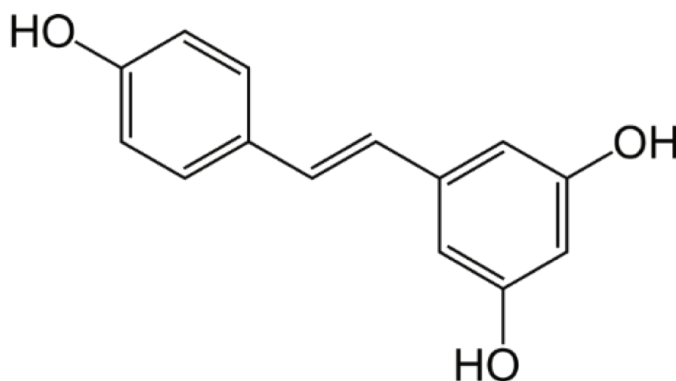


Figure 1. Chemical structure of resveratrol.

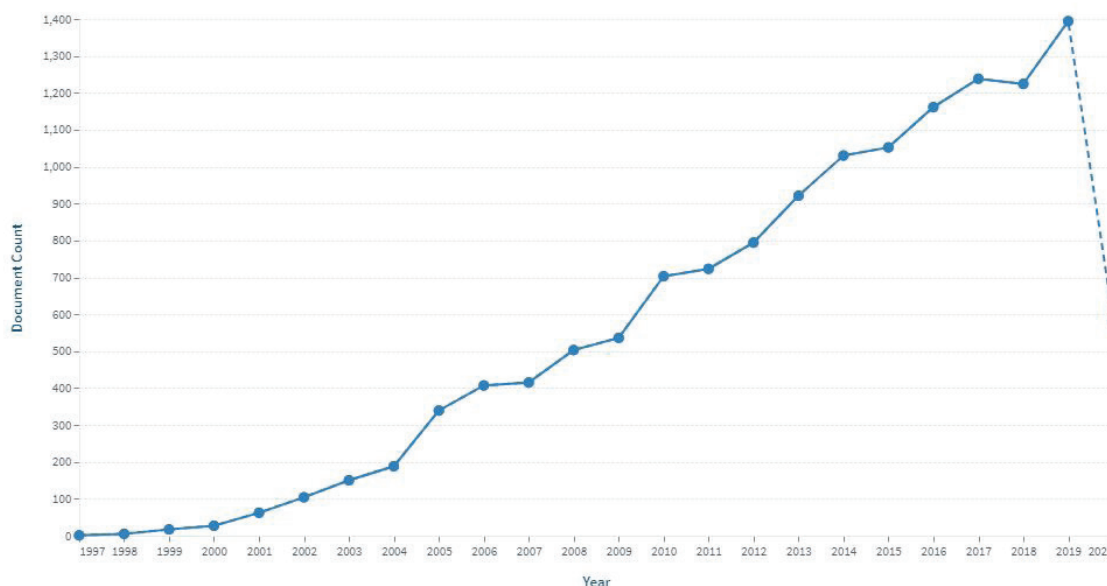


Figure 2. Number of patents filed with keywords “resveratrol” and “cancer” from 1997 to 2020. Data was obtained from *The Lens* patent search engine.

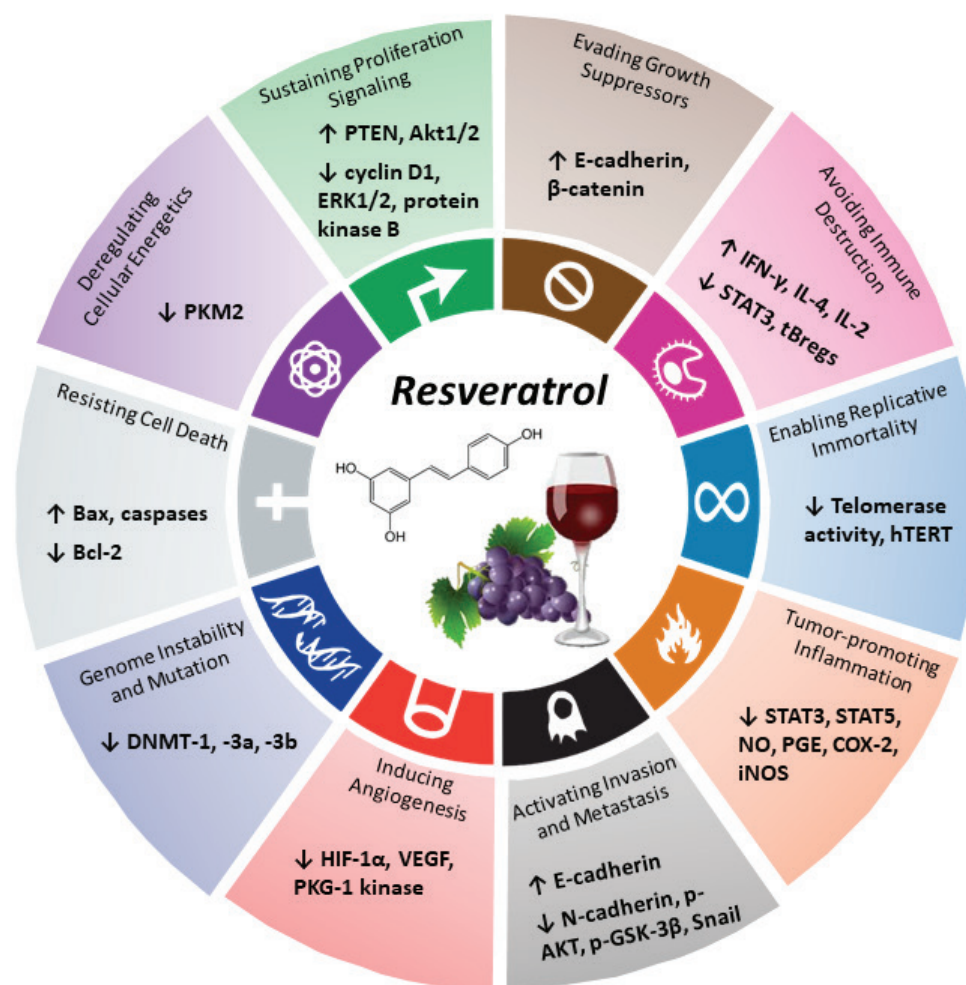


Figure 3. Cancer hallmarks and molecular targets modulated by resveratrol.

Prevention of Proliferative Signalling

Most cancer cells have upregulated proliferative signalling pathways in order to maintain their survival. The signalling pathways are often associated to the alteration in the expression of proteins related to cell cycle, metabolism and cell proliferation^[37–39]. RSV promoted the growth of ovarian cancer cell (OVCAR-3) by blocking PI3K and Akt signalling pathways, through reduction of phosphorylated extracellular signal-regulated kinase (ERK)1/2, downregulation of cyclin D1 and protein kinase B^[40]. Cancer cells have prevented the proliferation via activation of autophagy-suppressing pathway such as phosphatidylinositol 3-kinase (PI3K)/Mammalian Target of Rapamycin (mTOR)^[30]. Autophagy has become a target that may play an important role in cancer treatment. Studies have shown that RSV could induce autophagy cell death. Zhang and the research team proved that the treatment with RSV caused accumulation of calcium ions which then led to the activation of phosphorylated AMPK and phosphorylated Raptor via Ca^{2+} /AMPK-mTOR signalling pathway in the A549 human lung adenocarcinoma cells^[31]. The anti-proliferative effect of RSV has been determined in xenograft animal model (HCT116 colon cancer cells in athymic nude mice). The RSV induced the gene expression

of PTEN, the tumour suppressor gene, which then led to the downregulation PI3K/Akt signalling evidenced by the phosphorylation of Akt1/2^[32].

Activation of Growth Suppressors

On top of sustaining the proliferation, the cancerous cells are also overpowered the growth suppression pathway. There are two commonly known mechanisms of tumour suppressors, the retinoblastoma-associated (RB) and TP53 proteins. These proteins prevent the progression of cancerous cells growth through cell cycle arrest and cell death via induction of apoptosis. Evidence suggests that RSV induces cell death through the activation of p53 pathway, which further triggered apoptosis via mitogen-activated protein (MAP) kinases in T98G glioblastoma cells^[41]. The results were in congruent to with another study in which the p53-dependent apoptosis was activated due to the binding of RSV to integrin $\alpha\text{V}\beta\text{3}$, more specifically the β3 monomer^[42].

Research found that the abruption and suppression in the transforming growth factor β (TGF- β) and “contact inhibition” pathway which involve E-cadherin and epidermal growth factor (EGF) receptors has led to the proliferation of cancerous cells^[36]. Zhong *et al.* (2015)^[43] postulated that RSV suppressed the proliferation of OVAR3 ovarian cancer

cells by upregulated the protein expression of E-cadherin which subsequently increased the β -catenin on the cell membrane, leading to the inhibition of proliferation.

Promotion of Cancerous Cell Death

Normal cells maintain the homeostasis by programmed cell death through apoptosis. However, this normal cellular homeostasis is abrogated during tumorigenesis. Cancerous cells modulate the regulatory and effector components in the cell via increase the anti-apoptotic proteins such as Bcl-2 and downregulate the pro-apoptotic proteins such as Bax, Puma, Bim and caspases. Induction of apoptosis is considered as one of the strategies in cancer treatment due to the minimal inflammatory response^[18]. Convincing evidences showed that RSV induced apoptosis in various cancer cells such as T acute lymphoblastic leukaemia cell line^[44], HCT116 colorectal carcinoma cell^[45], Caco-2 colorectal cancer cells^[46], TRAMP murine prostate cancer cells^[33] and MCF-7 breast cancer cell^[34] through upregulation of Bax and downregulation of Bcl-2 expression. Some studies have suggested that the changes in the expression on both Bax and Bcl-2 were due to the disruption in the mitochondria membrane potential ($\Delta\psi_m$) after treatment with RSV^[33].

Apart from apoptosis, autophagy plays an important role in maintaining the cellular homeostasis by clearing up the aggregated proteins, damaged organelles or exogenous components via a lysosomal degradation process^[30]. Studies suggested that RSV could be a natural autophagy agent. Luyten and the research team found out that RSV induced autophagy via mTOR-dependent pathway with the presence of IP₃Rs and extracellular Ca²⁺ in HeLa human cervix carcinoma cells^[35]. The results is in compliance with Park *et al.* (2016)^[47] in which they suggested that RSV inhibited mTOR by directly docking onto the ATP-binding site of mTOR^[47].

Disabling Replicative Immortality

Telomeres have long been regarded as the guardian of genome stability. The telomere theory of aging and longevity of cells is well-recognised through its ability to elongate the DNA^[48]. Notwithstanding, the association of telomeres with cancer has been suggested in several studies that consistently demonstrated that the tumour cells contains higher percentage of telomerase activity as compared to normal cells. These observations strengthened the coherency that explains the immortality of cancerous cells. The understanding of the mechanisms underlying telomerase activity and telomere structures have offered another option for cancer therapy^[49]. Wang *et al.* (2011)^[50] reported that RSV delayed the senescence of endothelial progenitor cells isolated from human peripheral blood via the downregulation of telomerase activity. The study also suggested that the compound has regulated the expression of human telomerase reverse transcriptase (hTERT), the rate limiting component of telomerase activity, via the PI3K/Akt pathway^[50]. The results were in accordance to Mirzazadeh *et al.* (2017)^[49] in which they pointed out the role of RSV in regulating the replication immortality by inhibition of the hTERT

gene expression in a dose-dependent manner in human glioblastoma cell line U-87MG^[49].

Inhibition of Angiogenesis

One of the vital components for cancer development and progression is the formation of blood vessels (angiogenesis) in the tumour area. Cancerous cells regulate the pro-angiogenic factors such as vascular endothelial growth factor (VEGF) to stimulate vascular endothelial cells to enter the tumour hypoxic areas and anti-angiogenic factors such as thrombospondin-1 (TSP1) to inhibit the effect of VEGF^[51]. Studies showed that treatment with RSV has decreased the stabilisation of hypoxia-inducible factor-1 (HIF-1 α) which in turn downregulated the VEGF protein expression and upregulated the TSP1 protein expression in spheroid A375 melanoma cells^[52]. Another study by Mikula-Pietrasik *et al.* (2012)^[53] suggested that RSV suppressed the angiogenesis by downregulating IL-8/CXCL-8, the proangiogenic chemokine which regulated the expression of VEGF, in human peritoneal mesothelial cells (HUVEC, HMVEC and HMEC-1)^[53]. A combination of RSV with 5-fluorouracil (5FU) has enhanced the *in vitro* anti-angiogenic effect in B16 melanoma cells, as compared to treatment with either drug alone. The results demonstrated that the combined treatment has synergistically decreased the VEGF protein expression. As a proof of concept, further study was performed with B16 tumour-bearing BALB/c nude mice in the effort to assess the *in vivo* anti-angiogenic effect. After subcutaneous injection for 10 days, the combined treatment of RSV and 5FU has significantly decreased the VEGF protein expression with reduced microvessel density as compared to the negative control group^[54]. RSV has shown its anti-angiogenic effect by inhibiting the tube formation and cell migration in primary human vascular endothelial cells (HUVECs). The authors reported that the process was achieved by the suppression of PKG-1 kinase and four inhibitors of apoptosis proteins (c-IAP1, c-IAP2, livin and XIAP)^[55].

Deactivation of Invasion and Metastasis

Epithelial-mesenchymal transition (EMT) is a process where the epithelial cells lose the cell-cell contact by exhibiting mesenchymal phenotype. This process potentially worsen the prognosis in cancer patients by enhancing the invasiveness and migration of cancerous cells^[56]. Several studies have confirmed that RSV inhibited metastasis and invasion in various cancer cells through EMT signalling pathway^[57-59]. Yuan and team proved that RSV reversed EMT via regulation of AKT/GSK-3 β /Snail signalling pathway both *in vitro* colon cancer cells (SW480 and SW620) and *in vivo* lung metastasis animal model (SW480 tumor bearing nude mice)^[58]. The effect was verified using proteomic experiments, indicating that the treatment with RSV has upregulated the expression of E-Cadherin and downregulated the expression of N-cadherin, p-AKT, p-GSK-3 β and Snail in both models^[58]. Another key regulator, the metastasis-associated protein 1 (MTA1), is also known to correlate with the aggressiveness of the tumour metastasis. Li *et al.* (2013)^[60] has first demonstrated that RSV modulated the expression of MTA1-mediated proteins such as Ac-p53 in

prostate cancer xenografts animal model, consolidating the ability of RSV in deactivation of metastasis.

Epigenetic Modification

Epigenetic modification such as DNA methylation and histone modification are the important key regulators in affecting tumorigenesis^[61]. A number of research has been done to investigate the interaction of RSV with epigenetic targets such as DNA methyltransferase (DNMT), histone deacetylase (HDAC) and lysine-specific demethylase-1 (LSD-1) in regulating the histone proteins and DNA molecules^[62]. RSV showed its ability to reverse carcinogenesis by significantly reducing the DNMT mRNA expression (DNMT1, DNMT3a and DNMT3b) in human breast cancer cell lines (MCF-7 and MDA-MB-231), evidenced by Mirza *et al.* (2013)^[63]. Similarly, in combination of another plant-based pterostilbene, RSV has significantly decreased the activation of DNMT enzyme via restoration of oestrogen receptor- α (ER α) expression in ER α -negative breast cancer MDA-MB-157 cell line^[64].

Ameliorating the Tumour-Promoting Inflammation

Studies showed that 25% of the cancer occurred due to the chronic inflammation as a result of simultaneous destruction and healing of body tissues. Tumour-associated inflammation is always linked with poor prognosis^[65-67]. Signal transducer and activators of transcription (STAT) and NF- κ B signalling pathways are the two promising targets for cancer therapy as both collaboratively play role in inflammatory response via inducing the expression of pro-tumorigenic genes such as *IL-1 β* , *COX-2* and *cyclin D1*. Many studies have been focusing on the effect of polyphenols including RSV in tumour-associated inflammation. RSV has shown its efficacy by suppressing both STAT3 and STAT5 phosphorylation in 786-O renal cell carcinoma cells as evidenced by Kim *et al.* (2016)^[68]. It also co-regulated both STAT3 and NF- κ B pathways in medulloblastoma UW228-2 and UW228-3 cell lines, which subsequently lead to the up-regulation of Bcl-2 protein expression^[69]. Interestingly, RSV also regulated JAK-STAT pathway in colon cancer HT-29 cell line with significantly reduced expression level of nitric oxide, prostaglandin E₂, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), consolidating the effect of RSV in inflammatory process in various cancers.

Programming Energy Metabolism

Warburg effect was observed in cancer where the cells altered energy metabolisms, including increased glycolysis and lactate production, to cope with their growth requirements. Therefore, the proteins that are involved in the metabolism become the key elements in tumour progression and therapeutic targets for cancer treatment^[70-72]. Saunier *et al.* (2017)^[70] proved that RSV managed to reverse Warburg effect via activation of pyruvate dehydrogenase in colon cancer Caco2 cells. Interestingly, the reversal effect could be observed even with low doses of RSV that mimicked the drug concentration in human patients^[70]. Another study proposed that RSV modulated the Warburg effect via mTOR signalling pathway by down-regulation of

pyruvate kinase M2 (PKM2), a catalyst in converting the phosphoenol-pyruvate to pyruvate^[73], in cervical cancer HeLa, liver carcinoma HepG2 and breast cancer MCF-7 cell lines^[74].

Promotion of Immune Destruction

In normal cells, immune system acts as a surveillance to protect our body from against foreign microorganisms. In events where infection occurs, the immune system will initiate a series of mechanism to eliminate the source of infection. Principally, the immune cells could mount a response in eliminating the cancer cells which are recognised as “non-self”^[75]. However, the cancerous cells gain ability to alter the immune system through several mechanisms such as modulating the expression of major histocompatibility class (MHC1) or immunosuppressive products^[76](Print. Studies have suggested that RSV could modulate the molecular modulators of the inflammatory response *in vitro* and *in vivo*, via the activation of macrophage, T cells and natural killer^[77]. RSV suppressed the proliferation of cancerous cells via the secretion of IFN- γ , IL-4, IL-2, CD4+ in lymphocytes and elevated the secretion IL-10 via downregulation of the CD80 on macrophages^[78]. The compound was proven to enhance the expression of Fc γ RIIB, a receptor for IgG that blocks the activation of B cells in mice^[79]. As a result of the regulation of immune system, Lee-Chang *et al.* (2013)^[80] showed that RSV could inhibit the lung metastasis in 4T1-tumor bearing BALB/c mice via inhibition of phosphorylation of STAT3 and hence inactivation of tBregs^[80].

MOVING TOWARDS CLINICAL TRIALS

In order to realise the clinical translation for cancer therapy, the toxicity of RSV have been investigated to gauge its safety and effectiveness in both the animals and human. A commercialised RSV (ResVida) was found to have no-observed-adverse effect levels (NOAELs) of 750 mg/kg/bw in rats via oral administration, which then converted to human equivalent dose of 450 mg/kg^[81]. At higher dose of 3,000 mg/kg, oral administration of RSV does seem to caused renal and bladder toxicity after a daily administration for one month in rats^[82]. In human, the oral consumption of 5 g of SRT501, a proprietary micronised formulation of RSV by GlaxoSmithKline (GSK) for 14 days are well-tolerated in colorectal cancer patients^[83]. However, the toxicity seems to be largely affected by the pre-existing conditions of patients. For instance, one clinical trial that recruited subjects with multiple myeloma was prematurely terminated due to high incidence of renal toxicity after given a dose of RSV similar to SRT501. The patients had experienced an elevated serum creatinine level with more than 500 μ mol/L with minority developed crystal nephropathy and acute tubular damage^[84]. The toxic effect is believed to happen specifically to multiple myeloma patients which had developed pre-existing renal damage prior to the treatment.

A number of clinical trials have been conducted in recent decades to investigate the anti-cancer effect of RSV. Table 1 summarizes the clinical trials involved the use of resveratrol as a single therapeutic agent or combination therapy in cancer treatment:

Table 1. Clinical trials of resveratrol in cancer treatment, data retrieved from <https://clinicaltrials.gov/>.

Type of cancer	Phase and status	Treatment	Outcome	Ref.
Colon	Phase I (Completed)	- Oral administration of 20, 80, 160 mg/day of RSV - Two weeks treatment	Significant inhibition of the gene expression of Wnt target in colonic mucosa	[85]
Colon and Rectal	Phase I (Completed)	- Treatment is given after surgical resection - Oral administration of RSV for 9 days continuously (dose is not mentioned)	Outcome is not provided	-
Multiple Myeloma	Phase II (Terminated)	- Oral administration of 5.0 g SRT501 (RSV) for 20 days	The trial was terminated due to reported renal toxicity	[84]
Lymphangioliomyomatosis	Phase II (Recruiting)	- Escalating doses of RSV from 250 mg daily (for 8 weeks, 500 mg daily (8 weeks) and 500 mg twice a day (for 8 weeks) - (Route of administration is not reported)	Outcome is not yet reported	-
Polycystic ovary syndrome	Phase 4 (Recruiting)	- A combination treatment of 500 mg of RSV and 20 mg simvastatin daily - (Route of administration is not reported)	Outcome is not yet reported	-
Unspecific solid tumour	Phase I (Completed)	- Oral administration of 0.5, 1.0, 2.5, or 5.0 g RSV daily for 29 days	A decrease in level of IGF-I and IGFBP-3, suggesting RSV exhibits the chemopreventive property	[86]

CONCLUSION

Currently, the search and development of a more effective cancer therapeutic regimen with low toxicity and “broad spectrum” that could simultaneously target several mechanisms has been encouraged in response to the intolerable conventional chemotherapy. The cancer hallmarks have been adopted to provide a clear insight in understanding the potential of specific compounds as “dirty drugs” on the molecular basis. As can be seen, RSV was found to be interfering with all the cancer hallmarks and modulating the key signalling pathways in tumour development, hence suggesting that the compound hold a great promise for future anticancer drug development. On top of that, several studies have found that RSV exhibit synergistic anticancer effect when combined with other therapeutic agents. Even though the preclinical studies showed promising results, the compound has been disappointing with its toxicity and poor pharmacokinetics in human. We believe that RSV should be considered favourably as a broad-spectrum chemotherapeutic agent that might overcome the limitations of conventional treatment. The drug design and delivery formulation of this compound should be further improved for clinical translation.

Acknowledgements

The authors would like to acknowledge Monash Tropical Medicine & Biology (TMB) Multidisciplinary Platform and Monash Global Asia in the 21st Century (GA21) research grant (GA-HW-19-L-01 and GA-HW-19-S02) for this study.

Conflict of interest

The authors declare that there is no conflict of interest.

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