

THE OCCURRENCE OF RESVERATROL IN FOODSTUFFS AND ITS POTENTIAL FOR SUPPORTING CANCER PREVENTION AND TREATMENT. A REVIEW

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ABSTRACT

Over recent years, there has been increasing interest noted in those active substances derived from plants that show potential for preventing cancer development. The most promising candidate is resveratrol which can be found in large amounts in the skin of grapes, tomatoes and in red wine. Its beneficial effects on the human body are seen both in prevention and therapy. The anti-carcinogenic action of resveratrol is linked with its ability to neutralise reactive oxygen species and to modulate cellular processes such as apoptosis, and both cancerous cell proliferation and differentiation. This article presents the characteristics of resveratrol as a bioactive compound derived from natural sources exhibiting anti-cancer properties, which, because of a wide spectrum of biological activities may be used in the prevention of cancer. Many *in vitro* and animal-based studies have demonstrated such preventative anti-cancer action in the colon, prostate, breast and lungs. The beneficial effects of resveratrol are also presented when adopted as a support to conventional treatments of cancer using chemo- and radio-therapy.

Key words: *resveratrol, foodstuffs, chemo-prevention, cancer*

STRESZCZENIE

W ciągu ostatnich lat wzrosło zainteresowanie biologicznie czynnymi związkami pochodzenia roślinnego, które mogłyby ograniczyć rozwój chorób nowotworowych. Do najważniejszych z nich zalicza się resweratrol, występujący w większej ilości w skórce winogron, pomidorów i czerwonym winie. Resweratrol wykazuje korzystne oddziaływanie profilaktyczne i terapeutyczne na organizm. Przeciwnowotworowe działanie reswerastrołu związane jest z jego zdolnością do neutralizowania reaktywnych form tlenu oraz modulującym oddziaływaniem na procesy apoptozy, proliferacji i różnicowania komórek nowotworowych. Niniejsza praca przedstawia charakterystykę reswerastrołu jako związku bioaktywnego pochodzenia naturalnego o działaniu przeciwnowotworowym, który dzięki szerokiemu spektrum działania biologicznego może mieć zastosowanie w chemoprewencji nowotworów. Przeciwnowotworowa aktywność tego związku została dowiedziona w licznych badaniach *in vitro* oraz na zwierzętach, w których wykazano działanie zapobiegawcze reswerastrołu w stosunku do nowotworów: jelita grubego, gruczołu krokowego, piersi, a także płuc. Przedstawiono również jego korzystne oddziaływanie wspomagające standardowe leczenie nowotworów przy zastosowaniu chemioterapii i radioterapii.

Słowa kluczowe: *resweratrol, żywność, chemoprewencja, nowotwór*

INTRODUCTION

Cancer constitutes the main threat to global health. Effective methods for reducing such disease risks, or in ameliorating and slowing down the disease course is constantly sought for because of the significant social problems arising from its high morbidity and mortality rates; most frequently from cancers of the lungs, breast, colon, prostate, stomach and liver. Within the

last decade, there have been great advances made in understanding the molecular biology of cancer, nonetheless there have been no drugs discovered hitherto that can definitively cure/combat this disease. One the most promising avenues for reducing cancer disease is in chemo-prevention; a form of prophylactic measures based on employing natural or pharmacological agents for preventing, inhibiting or regressing carcinogenesis [75]. Many cell-based

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or animal-model based studies, along with clinical trials, have enabled natural bioactive substances to be selected from a normal diet which are potentially able to prevent or inhibit many cancers from developing [31, 54, 77]. These compounds are both able to neutralise carcinogens and their harmful effects brought about on the cell. Examples of secondary plant metabolites that possess anti-carcinogenic action are: carotenoids, glucosinolates, monoterpenes, phytosterols, polyphenols, saponins and lectins. Resveratrol is classified under polyphenols and is found in a number of fruit, and in copious amounts in the skin of grapes, tomatoes and mulberry fruit extracts. For many years, resveratrol has been studied *in-vitro* and in laboratory animals. Epidemiological and clinical studies have also been performed. This work presents a review on the properties, occurrence, dosages and mechanisms of resveratrol action against various types of cancer.

STRUCTURE OF RESVERATROL

Resveratrol (*trans*-3,5,4'-trihydroxystilbene) is a naturally occurring stilbenoid [19], consisting of two phenolic rings linked by an ethylene bridge, and is considered as belonging to the phytoestrogens. It is a white powder, insoluble in water but soluble in ethanol [2]. Resveratrol exists as two geometrical isomers: *trans*- and *cis*- (Figure 1) [24, 47]. The *trans*-resveratrol form has the greater stability and biological activity [80], however the *cis*-form arises from isomerisation of the *trans*-form following breakdown of the resveratrol polymer molecule due to the action of UV light during the fermentation of grape skins, or by being under high pH conditions. Both forms are present together in wine along with gallic acid and other antioxidants. [38]. A number of naturally occurring or synthetic resveratrol analogues are also recognised that differ in the type, number and the positions of their substitutions [2].

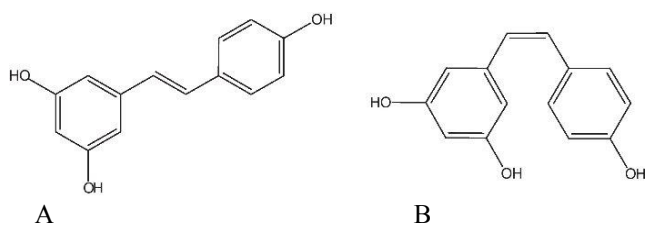


Figure 1. Chemical structure of resveratrol: A - *trans*-form, B - *cis*-form [24, 53]

OCCURRENCE OF RESVERATROL

Resveratrol is phytoalexin which up till now has been detected in 72 types of plants. It was first isolated in 1940 from the root of the white opuntium plant (*Veratrum grandiflorum* O. Loes) [2]. A rich source has been found to be the root of the knotweed, as cultivated

in China and Japan. Another source are grapes which contain varying amounts of this compound; Table 1, [53, 60]. Black grapes are the best source of resveratrol, whilst red grapes have more of this substance than the green varieties. Resveratrol is particularly abundant in grape skins [5, 49, 53, 61]. The highest amounts of the *trans*-3,5,4'-trihydroxystilbene form are found in the red Pinot Noir grape varieties [50]. In similar fashion to grapes, levels of this substance vary greatly in grape juice and wine, (Table 1) [21, 66], according to grape variety and the place of cultivation [77]. UV light stimulates the formation of resveratrol as well as do other factors such as the agrotechnical and the climatic, together with any stressful conditions that affect plants like pathogenic attack (bacterial or fungal) or by mechanical damage [21, 59]. Red grape wines contain more resveratrol than rosé or white wines, mainly resulting from the different types of manufacturing and the diverse varieties of grape [1]. Higher resveratrol concentrations are observed in organic wine [16]. In Poland, resveratrol concentrations vary from 0.39 to 4.45 mg/L in commercially available wines [62]. This compound can also be found in fruit berries, breadfruit, apples, nuts and in some herbs, (Table 1) [88]. It is also present in cocoa and chocolate [33, 49, 63]. The resveratrol composition measured in selected foodstuffs by various studies is presented in Table 1, [42, 53, 62, 66, 68, 80]. Exceptionally high levels are found in mulberry fruit extracts along with the seed extract from the exotic Jamun fruit [73]. Resveratrol has been found in the leaves and flowers of plants like orchids, scots pine and rhubarb [18], and furthermore it is synthesised by some trees such as eucalyptus and the spruce.

DOSAGE AND HEALTH SAFETY

Resveratrol is absorbed into the body via the small intestine and then becomes rapidly metabolised in the hepatocytes. Indeed, *in vitro* studies have shown that practically all resveratrol is metabolised in this way by humans [60, 62, 67]. It is recognised as being a safe and well tolerated substance at intakes of 5 g daily [58], however at levels of 2.5 and 5 g it can lead to mild to moderate symptoms appearing in the gastrointestinal system [11, 76]. A study by Patel et al. [57] suggests that 0.5 and 1.0 g of daily resveratrol is sufficient to elicit pharmacological action in the human gastrointestinal system. No side effects at intake levels below 1 g daily were observed in another study [76]. A multiple dose study demonstrated mild side effects, chiefly headaches, when 25, 50 100, 150 mg were given every 4 hours over a 48 hour period [4].

Resveratrol originating from the Japanese knotweed (*Polygonum cuspidatum*) has been used over many years throughout countries of the EU,

where dietary supplements are commercially available as derived from grapes and grape seeds, containing single 200-500 mg portions of resveratrol. Since 2012, permission was granted for the market placement of resveratrol manufactured from genetically modified yeast (*Saccharomyces cerevisiae*) as a novel food containing a maximum allowable dose of 500 mg/24 hours [20]. Over the last 10 years, there have been around 40 types of dietary supplements introduced onto the market in Poland that contain resveratrol. The main source of resveratrol in such products are grapes in the form of extracts from the fruit skin or seeds, but also from the roots of the Japanese knotweed; the resveratrol content in these supplements ranging between 50-250 mg. A study by *Ortuno et al.* [56] however showed a six-fold higher bioavailability of resveratrol when originating from natural grape products as compared to the resveratrol found in dietary supplements. It is estimated that the daily dietary intake of resveratrol per person in the EU from naturally occurring sources is on average 0.46 mg, whereas the highest of such daily intakes was recorded in elderly patients at 2.93 mg [20].

Table 1. Resveratrol content in chosen foodstuffs according to published studies

Foodstuff	Resveratrol content	Literature source
Lingonberry	5.88 µg/g d.m.	[66]
Grapes	6.47 µg/g d.m.	[66]
Fresh grapes	0.16-3.54 µg/g	[53, 61]
Peanuts and pistachios	0.02-1.79 µg/g	[62, 80]
Raw peanuts	0.09-0.30 µg/g	[42]
Roasted peanuts	0-0.13 µg/g	[42]
Grape skin	50-100 µg/g	[5]
Dried grape skin	24.06 µg/g	[53, 61]
Plum skin	0.1-6.2 µg/g	[68]
Tomato skin	18.4±1.6 µg/g d.m.	[63]
Mulberry fruit extract	50.61 µg/g d.m.	[73]
Grape seed extract	5.89 µg/g d.m.	[73]
Grape skin extract	3.54 µg/g d.m.	[73]
Cranberry juice	0.2 mg/L	[53]
Red grape juice	0.5 mg/L	[61]
Grape juice	0.45-2.60 mg/L	[81]
Grape juice	0.003-14.50 mg/L	[65]
Wine	0.1-14.3 mg/L	[21]
Cocoa	1.85±0.43 µg/g	[33]
Bitter chocolate	0.35±0.08 µg/g	[33]
Milk chocolate	0.10±0.05 µg/g	[33]
Milk chocolate	0.35±0.08 µg/g	[33]
Peanut butter	0.27-0.70 µg/g	[42]

ANTI-CANCER ACTION

Resveratrol is a compound that demonstrates a comprehensive range of chemo-preventative and chemo-therapeutic actions. Its anti-cancer properties arise from anti-oxidative, anti-inflammatory, anti-mutagenic, anti-carcinogenic and anti-proliferative characteristics [19, 77]. The anti-cancer action of resveratrol is, above all else, achieved by inhibiting the proliferation of cancerous cells, initiating apoptosis and modulating the action of a range of pro- and anti-apoptosis factors which affect apoptosis, differentiation of cancerous cells, reducing inflammatory reactions and neutralising free radicals [15, 19, 31, 54].

The mechanism underlying the chemo-preventative action occurs in two ways and is divided into two categories: blocking factors (acting at the initiation stage) and suppression factors (modulating stages of cancer promotion or progression) [5]. Because of its wide spectrum of biological activity, resveratrol is able to block every stage in the process of cancer development, ie. initiation, promotion and progression by means of modulating the signalling transduction pathways [5, 31, 74, 75]. Resveratrol can block the initiation phase of the tumour formation process; primarily through its ability to remove free radicals. Resveratrol exerts a protective effect, preventing lipid peroxidation and DNA damage by reactive oxygen species, thus in turn limiting cell mutation processes [3, 30]. In the promotion phase, resveratrol reduces the activity of cytochrome P-450 (CYP) compounds and inhibits their transcription. Cytochromes are involved in free oxygen radical formation which thereby cause increased activity of carcinogenic factors [67]. Resveratrol reduces the expression and activities of the CYP1A1, CYP1A2 and CYP1B1 enzymes and thus affords cellular protection against the action of many carcinogens; for example by polycyclic aromatic hydrocarbons [9, 47]. As an antioxidant, resveratrol prevents normal cells from being transformed into cancerous ones [50]. In the last and third phase of tumour development, resveratrol silences various cancer cell lines by partially inhibiting both DNA polymerases (an enzyme catalysing DNA synthesis) and ribonucleotide reductase (an enzyme vital for DNA synthesis in dividing cells). In addition, resveratrol inhibits the proliferation of tumour cells and DNA replication, inducing cellular apoptosis, thereby helping the removal of damaged or spent cells [88].

Throughout many years, resveratrol has been the subject of numerous biochemical, clinical and epidemiological studies which have confirmed its chemo-preventative action. Studies that confirm the anti-tumour action of resveratrol are mainly on the colon, prostate, lungs, breast and ovaries. Emerging

outcomes from clinical studies on human subjects confirm those findings, based on *in-vitro* studies on laboratory animals within the last ten years, which show that resveratrol also has a significant potential for improving health and preventing chronic disease in humans [77].

CANCER OF THE COLORECTAL CANCER

Many studies on animals and humans demonstrate the chemo-preventative action of resveratrol on tumours of the colon. An *in vitro* study by *Wolter et al.* [85] showed that resveratrol is able to inhibit the colonic cancer cell cycle. The anti-cancer action of resveratrol has also been demonstrated in animal models as well as in human clinical studies [47]. Experiments on animals predisposed to developing intestinal cancers have shown that this compound inhibits the proliferation of tumour cells [71]. The effect of grape extracts on blocking cancer has been studied in humans. Patients diagnosed with colorectal cancer after successful tumour resection were given a grape extract over 14 days containing relatively low doses of resveratrol ranging 0.073-0.114 mg. Nonetheless, those genes responsible for cancer development became inhibited in such patients. Further studies were performed using higher resveratrol doses of around 500 mg to 1 g, where decreases in cancerous cell proliferation of the colon was shown to be dose dependent [62]. In another study, healthy subjects received 500 mg to 5 g doses of resveratrol for 29 days where blood testing demonstrated, regardless of the administered dose, decreased production of IGF-1 (insulin-like-growth-factor 1) and IGFBP-3 (insulin-like-growth-factor-binding protein 3) growth factors, which are associated with the development of cancer [15]. A recent clinical study by *Yang et al.* [87] however confirmed that resveratrol inhibited colorectal cancer cell proliferation in a time and dose dependent fashion. Resveratrol's protective role in colorectal cancer is linked to modulating gene expression through its effects on p21 and Bax proteins [47]. Resveratrol induces cell apoptosis with the participation of the p53 tumour suppressor [17]. *Ji et al.* [35] demonstrated that resveratrol inhibits metastasis of colorectal cancer, both *in vitro* and *in vivo* in mice. Upon studying the effect of micronized resveratrol (SRT501) in patients with colorectal cancer metastasised to the liver, *Howels et al.* [32] showed that the micronisation increased the absorption of this compound, thereby increasing its bioavailability. They demonstrated the usefulness of this form of resveratrol as a potential agent for preventing cancer in those organs distant from the site of absorption.

PROSTATE CANCER

In vivo studies have shown that resveratrol blocks tumour growth in athymic mice by inhibiting

angiogenesis and increasing apoptosis in xenograft LNCaP cells. It also prevents cancer progression and growth in TRAMP mice (a prostate cancer animal model) and reduces the expression of androgen receptors in tumour cells [69]. It was shown that resveratrol's antitumor activity was elicited through its effects on the cell cycle, apoptosis, angiogenesis, metastasis, tumour invasion, as well as on other signal transduction pathways; eg. NF-kappaB, MAPK EGF in the prostate cancer cell [2, 64]. Resveratrol blocks the cell cycle and induces cytotoxicity and apoptosis in prostate cancer cells [93]. Studies by *Ganapathy et al.* [25] on prostatic cancer cells have confirmed that resveratrol may enhance the proapoptotic potential of TRAIL (TNF-Related Apoptosis Inducing Ligand); a cytokine capable of inducing apoptosis in cancer cells which is of low toxicity to untransformed cells. In the cell lines investigated, 60% of tumour cells were sensitive to TRAIL-induced apoptosis. Upon subjecting PC-3 cells (prostate cancer cell line) to resveratrol action in mice, angiogenesis became blocked in similar fashion to the effect of TRAIL. Fewer numbers of capillaries were found in tumour tissue and there was decreased expression of VEGF and VEGFR2 (vascular endothelial growth factor) as well as the metastatic matrix metalloproteinase markers (MMPs); MMP-2 and MMP-9. Elevated MMPs expression is related to an increased potential of metastases occurring in various types of cancerous cells. Resveratrol also inhibits cytoplasmic phosphorylation of the transcription factor FKHRL 1 (Forkhead Homolog Rhabdomyosarcoma Like 1), thus causing its activation and raising its ability to bind with DNA [52]. These aforementioned studies suggest that resveratrol may block the growth of prostatic cancer, the development of metastases and angiogenesis, along with perhaps being effective in the actual treatment of this condition. A study by *Kumar et al.* [39] confirmed the anti-tumour effect of resveratrol and its analogues on prostate cancer arising from their regulation of the chromatin modifier MTA1 (Metastasis-associated protein 1) and microRNA (miRNA). Anti-cancer effects were demonstrated on prostate cancer by both natural and synthetic analogues of resveratrol: pterostilbene, trimethoxy-resveratrol, piceatannol, diacetyl-resveratrol (2AC-Res, *trans*-3,5-diacetylstilbene), triacetyl-resveratrol (3AC-Res, *trans*-3, 5,4'-triacetylstilbene) and dimethoxystyryllaniline (DMSA, *trans*-4-(3,5-dimethoxystyryl) aniline).

LUNG CANCER

Animal studies have shown a significantly reduced proliferation of lung cancer cells transplanted into mice upon oral administration of resveratrol glycosides [37]. Other studies on the lymphocytes of both healthy and lung cancer patients have revealed

that resveratrol reduces the expression of cytochrome P450 (CYP1) isoenzymes in a dose-dependent manner under basic conditions, as well as after induction with benzo[a]pyrene and an extract of tobacco smoke. Such findings suggest that resveratrol may prevent or delay cancer development in tobacco smokers and to also confirm both its inhibition of cytochrome P450 isoenzymes which participate in phase I reactions, as well in stimulating the phase II metabolizing enzymes [50]. An *in-vitro* study by Zhang et al. [89] found that the 3,4'-trihydroxy-trans-stilbene resveratrol analogue induces apoptosis and autophagy in lung cancer cells.

BREAST CANCER

Studies by Gehm et al. [29] concluded that appropriate concentrations of resveratrol are needed to block oestradiol binding to oestrogen receptors in human breast cancer cells. In some cells, this compound functions as a 'super-agonist', where it has a higher activity than oestradiol, whilst in other cell types it exhibits an equal or lowered agonist activity as compared to oestradiol. It was suggested that resveratrol, which displays phyto-oestrogenic properties, regulates the expression of many genes directly associated with breast cancer development, amongst which are included the BRCA1 suppressor gene [41], as well as decreasing carcinogen DMBA-induction (7,12-Dimethylbenz[a]anthracene) of preneoplastic lesions in cultures of murine breast cells [48]. According to Laux et al. [40] resveratrol induces apoptosis of breast cancer cells by means of p-53 protein dependent signalling pathways. The anti-tumour effect can be linked to the inhibition of COX-2 and MMP-9 (matrix metalloproteinase-9) enzymes involved in the formation of metastases and NFκB, which mediates proliferation [8]. The chemotherapeutic properties of resveratrol in breast cancer were confirmed in murine studies showing reduced tumour growth, decreased angiogenesis and an increased apoptosis rate, achieved through reducing levels of VEGF endothelial growth factor and modulating progesterone receptor expression [28]. A study investigating the effect of resveratrol on the course of DMBA induced tumours in mice showed that dietary resveratrol is particularly beneficial. Indeed, when giving a resveratrol enriched diet to animals, cancer morbidity becomes reduced [10]. Whitsett et al. [84] also showed that DMBA treated rats when given dietary resveratrol at 1 g/kg inhibited cancer by reducing the number of tumours developing and extending the time of their suppression.

OVARIAN CANCER

Numerous studies have been conducted on the anti-tumour properties of resveratrol on ovarian

cancer cells which have demonstrated its inhibitory effects on tumour cell growth. The biochemical and morphological changes underway in tumour cells suggest more of an autophagocytosis process than apoptosis. The former may constitute a second mechanism of cell death induced by resveratrol which is apoptosis independent [55, 70]. Zhong et al. [90] investigated the effect of resveratrol treatment on two human ovarian cell lines, OVCAR-3 and Caov-3, which clearly demonstrated a marked inhibition of accumulation in the G1 phase, increased apoptosis and a simultaneous suppression of STAT3 (Signal transducer and activator of transcription 3). It was concluded that resveratrol is a promising candidate for treating ovarian cancer. Resveratrol inhibited glucose uptake in murine studies and significantly affects anti-tumour action through inhibiting ovarian tumour growth [78]. The latest *in-vitro* studies have shown a beneficial effect of a new derivative of resveratrol, 3,3',4,4'-Tetrahydroxy-trans-stilbeneon, on ovarian cancer by increasing apoptosis rates, inhibiting proliferation but accelerating cancer cell aging. It may thereby prove to be an invaluable supporting tool for combating ovarian cancer [51].

OTHER CANCERS

Apoptosis in cancer cells has been shown to be induced by resveratrol in cases of neuroblastoma, which is a very aggressive cancer suffering from a particularly poor prognosis at its advanced stages [45]. Other studies have observed a beneficial effect of resveratrol in treating B-cell lymphoma [12], non-Hodgkin's lymphoma [34], medulloblastoma - medulloblastoma [82], prostate cancer [27] and gastric cancer [26]. In a study on rats receiving N-nitrosomethylbenzamine (an oesophageal cancer provoking factor), the applied resveratrol doses of 1 or 2 mg/kg reduced both the number of tumours and their size [43]. Kalra et al. [36] indicated that resveratrol induces apoptosis in mouse skin tumours, suggesting chemo-preventive action through modulating those proteins involved in the mitochondrial pathway of apoptosis. Resveratrol induces the expression of pro-apoptotic Bax and p53 proteins, contemporaneously reducing anti-apoptotic Bcl-2 protein. Reducing the melanoma tumour growth due to resveratrol was confirmed in a murine study by Carletto et al. [14], which demonstrated a higher effectiveness when using a nanocapsule formulation. Resveratrol was observed to afford modulated protection against UVB radiation; this being the main cause of non-melanoma skin cancer [6]. It also diminishes the number of liver cancer cells and reduces the incidence of hepatitis B in HCC-infected mice (hepatocellular carcinoma) [47]. Resveratrol suppresses the formation

of reactive oxygen species and stimulates the growth of hepatocytes which replace damaged liver cells and supports their regeneration [44]. *Cai et al.* [13] have shown resveratrol to inhibit proliferation and induce apoptosis in a nasopharyngeal cancer cell line. Studies on the expression of 2,059 genes with potential links to the development of renal cell cancer examined the effect of giving resveratrol and showed that this compound may have very powerful and dose dependent anti-tumour action [72]. Recent studies indicate that resveratrol inhibits proliferation of pancreatic cancer cells, eliciting apoptosis and halting the cell cycle. It also stops metastasis, and thereby can be regarded as a potential anti-tumour agent in the treatment of pancreatic cancer [19, 86]. *Gao et al.* [46] found that resveratrol inhibits the Hh (hedgehog) and EMT (Epithelial mesenchymal transition) signalling transduction pathway and also inhibits tumour invasion and metastasis of gastric cancer *in-vitro*. The latest studies on the synthetic analogs of resveratrol have demonstrated their powerful anti-cancer action which may be used in the future treatment of leukaemia arising from their inhibitory effect on the polymerisation of tubulin.

RESVERATROL, A SUPPORTIVE FACTOR FOR CHEMO- AND RADIO- THERAPIES

Fulda and Debatin [23] found resveratrol to be a potent factor for sensitising cells to chemotherapeutic agents used in oncological treatment; for example in lung cancer. Initial treatment with resveratrol appears to inhibit the cell cycle during the S phase, which promotes induction of cellular apoptosis caused by the given medication. Such findings were also confirmed in studies where three malignant melanoma cell lines were isolated, with different levels of resistance to chemotherapeutics, and then subjected to resveratrol. Significant inhibition of tumour cell growth was observed together with cell cycle disruption, resulting in a sensitisation to standard treatment. It was suggested that this compound may become one of the adjuvant drugs used in treating advanced cases of melanoma [22]. When used at high doses, resveratrol sensitises cancer cells to X-rays when treating cases of cervical cancer, in chronic myeloid leukaemia and erythema in multiple myeloma. It was also shown to decrease the formation of free radicals in pancreatic cancer cells when administered together with radiation. Nevertheless in this last case, mitochondrial function became compromised when only resveratrol was given without any exposure to radiation [7]. Other studies found that resveratrol causes apoptosis by depolarising the mitochondrial membrane potential in the those β -cells of acute lymphoblastic leukaemia resistant to radiotherapy [67].

SUMMARY

As a natural ingredient in foodstuffs, numerous studies have demonstrated that resveratrol possesses a very high anti-oxidant potential, exhibits anti-tumour action as well as being a likely candidate agent for the prevention and treatment of several types of cancer. Its anti-cancer properties have been confirmed by many *in vitro* and *in vivo* studies which show that resveratrol is able to inhibit all stages of carcinogenesis; ie. initiation, promotion and progression. The anti-tumour action arises mainly from effects such as anti-inflammatory, anti-oxidant, pro-apoptosis and anti-proliferative actions. Many studies have provided much evidence that resveratrol not only acts a chemo-preventative agent, but also possesses chemo-therapeutic properties. *In vitro* work has shown that resveratrol enhances the effectiveness of chemotherapy through inactivating NF- κ B protein (a transcription factor) that is formed by cancer cells and which controls the expression of certain genes. When this factor is present, cancer cells become resistant to chemotherapy which then allows them to multiply. Resveratrol blocks this transcription factor, thereby enabling chemo-therapeutics to act at their targeted sites [88].

Animal experiments, along with clinical studies have shown the anti-carcinogenic action of resveratrol in instances of the following cancers: colon, prostate, lungs, breast and ovaries [77]. Apart from its preventative effects, many workers have demonstrated chemo-therapeutic action by increasing the efficacy of traditionally used chemotherapy and radiotherapy. Studies have found that resveratrol is a powerful agent for sensitising cells to chemotherapy used for oncological treatment that includes cancers of the lungs, cervix, chronic myeloid leukaemia, multiple myeloma and the prostate. Resveratrol is a natural product commonly found in food supplements which can be singly used or in supporting treatment. It is a natural and biologically active substance, safe to use, and thus should be much more widely consumed in those natural products rich in this ingredient and/or as dietary supplements, where it occurs in a concentrated form at higher levels (1 g/day). There is therefore a need to promote knowledge of resveratrol's beneficial pro-health and anti-tumour effects. Conventional cancer treatment with chemotherapy should be supported by an increased consumption of this substance from foodstuffs that contain natural amounts as well as via dietary supplements.

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