Resveratrol: Biological Activities and Potential Use in Health and Disease

Gianfranco Risuleo and Camillo La Mesa

Abstract

Resveratrol (RV) is a polyphenol non-flavonoid compound present in strongly pigmented vegetables and fresh fruits as well as dried nuts such as peanuts. High concentrations of this natural compound were found, in the modern occidental world, in the peel of the berries of the red grape *Vitis vinifera*, but usage of this natural drug in popular medicine has been documented much earlier. Resveratrol exhibits diverse biological activities such as antitumor, antioxidant, antiviral, and phytoestrogenic. In particular, as the work reported from our laboratories, the compound shows an inhibitory effect on murine polyomavirus DNA replication, while at higher concentrations, RV shows a significant cytotoxic effect. This complex dose-dependent behavior is not intrinsic to the drug. Other natural substances behave in a similar way, curcumin and a semi-purified fraction of the whole neem oil being two different examples. Most likely, the administration of RV to cultured cells alters the permeability and fluidity of the cell membrane. Also, data presented in literature ascribe to RV an antiproliferative action, thus rendering this drug a good candidate for the control of neoplastic growth. The potential usage of RV both in human and veterinary medicine is also examined in this review.

Keywords

Resveratrol · Nutraceutical · Veterinary nutraceutical · Biological properties · Potential applications · Advanced medicine

"Gianfranco Risuleo" is on retirement.

G. Risuleo (✉)
Department of Biology and Biotechnologies "Charles Darwin", Sapienza University of Rome, Rome, Italy
e-mail: gianfranco.risuleo@uniroma1.it

C. La Mesa
Department of Chemistry "Stanislao Cannizzaro", Sapienza University of Rome, Rome, Italy

1 Prologue

The expression "the research on natural compounds and nutraceuticals is in a continuous and ever growing expansion" may sound overused, if not abused and trivial. But, just to give the reader an example about the validity and timeliness of this saying, we will report on a result easily acquired from a simple and quick literature database search. When one of us (G. R.) was invited to write a chapter for a book on *Nutraceuticals: Efficacy, Safety and Toxicity*, back in 2016 (Risuleo 2016), the number of review articles published, from the 1960s of last century up to 2014, on the general subject "natural substances and their biological activities," was about 1650. Now the same search using simply **resveratrol**, as a keyword, yields an amazing 1560 entries (only in terms of review articles) from 2001 up to the present days. It is easy to assert, therefore, that the general interest on this topic has not at all dwindled but remains a central theme for the research in alternative commodities, foodstuffs, and, last but not least, drugs aimed at therapeutic usages.

In this condensed chapter, we shall focus on resveratrol as a potential medicinal remedy in the human and veterinary field. In any case, an overview on the biological properties of resveratrol is necessary. We deliberately kept the language very plain and comprehensible also to scientists not necessarily or directly engaged in biomolecular/physical research on natural compounds, as well as to the layman and people interested in alternative ways to look at nutrition and health care. As a matter of fact, we are convinced that a subject raising such a vivid attention should be easily accessed by everybody.

2 Introduction

2.1 Phytoalexins in a Nutshell

Phytoalexins are natural compounds endowed of antimicrobial and antioxidative action; they include molecules like terpenoids, glycosteroids, and alkaloids. They are synthesized

R. C. Gupta et al. (eds.), *Nutraceuticals in Veterinary Medicine*, https://doi.org/10.1007/978-3-030-04624-8_15

de novo by plants under stress conditions which may originate, for example, by a pathogenic attack and/or by physical adverse conditions, e.g., drought. Pathogen infection may cause a rapid accumulation of phytotoxic substances, at the site of infection: here, phytoalexins show their character as broad-spectrum inhibitors of the infectious progression. The family of phytoalexins has manifold chemical characteristic and includes terpenoids, glycosteroids, and alkaloids. In any case, the definition of phytoalexin is applied to all types of phytochemical molecules involved in the plant defense: in a very broad sense, their action could be compared to the animal immune system. As a matter of fact, the susceptibility of the plant tissue to infection increases when the biosynthesis phytoalexin is inhibited. With respect to this, authors showed that plant mutants incapable of producing these natural "defenders" are more vulnerable to pathogen colonization as compared to wild type; conversely, host-specific pathogens able to degrade phytoalexins cause a higher virulence toward the plant (Glazebrook and Ausbel 1994; Thomma et al. 1999).

As mentioned above, polyphenols, flavonoids, and chemically related substances play a key role in the defense against fungal and other pathogens. We shall mention here a few examples of these "plant-protective" molecules:

Danielone is a phytoalexin found in the fruit of the papaya plant (*Carica papaya*) showing a potent antifungal activity against *Colletotrichum gloeosporioides*, an infectious pathogenic fungus (Echeverri et al. 1997).

Sakuranetin is a flavanone found in rice and other exotic plant like *Polymnia fruticosa* where it inhibits the germination of the spores of *Magnaporthe grisea* (Molnár et al. 2010; Cho and Lee 2015). Finally, it has been suggested that in *Sorghum*, the interactions with the abovementioned *Colletotrichum* seem to be inhibited by the expression of the SbF3'H2 through the synthesis of the pathogen-specific phytoalexins 3-deoxyanthocyanidin (Shih et al. 2006) whose gene encodes a flavonoid 3′-hydroxylase.

Stilbenes are produced in *Eucalyptus sideroxylon* in case of pathogens attacks. Such compounds can be implied in the hypersensitive response of plants. Actually one of the reasons why some woods show a natural preservation against rot may reside in the presence of high levels of polyphenols as reported by a "classical" work by Hart and Hillis (1974).

Finally, going back to the main subject of our work, also resveratrol belongs to the chemical family of phytoalexins. In particular *trans*-resveratrol in *Vitis vinifera* grapes is produced by the plant to combat the infection and proliferation of fungal pathogens such as *Botrytis cinerea* (Favaron et al. 2009). Figure 1 shows the structures of some common phytoalexins with different chemical features.

From what we have briefly discussed above, it is clear that the importance of these molecules goes beyond the intrinsic scientific interest and derives also by their enormous commercial significance. In fact phytoalexins may be considered very important to counteract plant disease and more in general in pest control.

This brief overview on phytoalexins, however, is far from being exhaustive; the reader who wants to deepen this subject should refer to reviews dealing specifically with this matter. See for instance: (Harborne 1999; Ahuja et al. 2012; Großkinsky et al. 2012; Sanchez Maldonado et al. 2015; Meyer et al. 2016; Oliveira et al. 2016; Burow and Halkier 2017; Santos Silva et al. 2018).

2.2 Resveratrol: The Molecule and Its Synthesis

As mentioned above, resveratrol is a phytoalexin of natural origin produced by both bryophytes and higher plants in response to stimuli of different nature. Resveratrol is a stilbenoid with a low molecular weight (MW = 228,25 dal); it is characterized by two aromatic rings linked by an ethane or ethylene residue. The aromatic rings that compose it present three hydroxyl groups at positions 3′, 4′, and 5′. In the IUPAC nomenclature is classified as 5-[(*E*)-2-(4-idrossiphenil)-ethenil] benzene-1,3-diol, but it is also known as 3,4,5 tri-hydroy-stilbene or 3,4,5 stilbene-triol.

In plants, the synthesis of RV is mediated by the enzyme, resveratrol synthase (Schröder et al. 1988). The drug is normally found in two geometric isomer forms: *cis*-(*Z*) and *trans*-(*E*) resveratrol; both isomers can exist in a free or glucose-bound form. The *cis–trans* isomer transition occurs by photoisomerization, a process mediated by UV-light (Mattivi et al. 1995; Lamuela-Raventos et al. 1995) (Fig. 2).

Resveratrol is water soluble up to a concentration of 16.9 mg/L at 25 °C, but solubility is higher in ethanol. Its melting temperature is 253 °C. In addition, the *trans*-resveratrol powder is stable at 40 °C in the presence of air and in a relatively dry atmosphere (75% humidity). This isomer is also stabilized by the presence of transport proteins (Prokop et al. 2006, see also below). The commercially available preparation consists of a white powder with a yellowish-orange hue.

Resveratrol is synthesized in *Vitis vinifera* following the metabolic pathway of the phenyl-propanoids (Dixon and Paiva 1995) where the starting compound is phenylalanine. The enzyme phenylalanine ammonium lyase mediates the elimination of the NH2 group from the amino acid and catalyzes the formation of cinnamic acid: the series of metabolic steps leading to the synthesis of RV is shown in Fig. 3 (reproduced

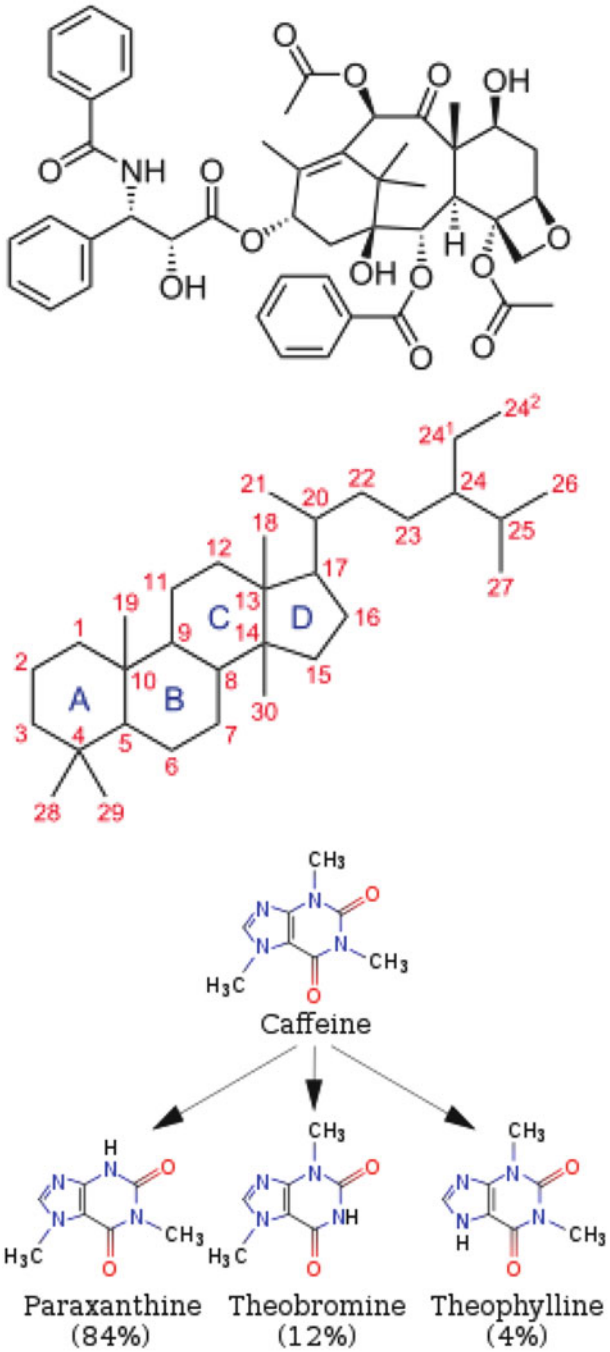

Fig. 1 Structure and function of some common natural substances. Top panel: The terpenoids, also known as isoprenoids, derive from terpenes which are hydrocarbons with additional functional groups, usually containing an oxygen atom. They form a large and diverse class of natural organic chemicals. About 60% of known natural products are terpenoids. The figure reports the chemical structure of the terpenoid taxol, a well-known anticancer drug obtained from the tree *Taxus baccata* and now produced also in laboratory in plant cell culture systems. Center panel: Steroids are biologically active organic compounds with four rings arranged in a specific molecular configuration. They are important components of cell membranes playing a role in membrane fluidity. They may also function as signaling molecules. A large number of steroids are found in plants, fungi, and animals. Bottom panel: Alkaloids can be purified from crude extracts by acid-base extraction by bacteria, fungi, plants, and animals. They show a very broad range of pharmacological activities. Unlike other natural compounds, alkaloids are characterized by a great structural and functional diversity; therefore their univocal classification is almost impossible. Obsolete methods have classified alkaloids by the common natural plant source. This was due mainly to lack of knowledge about their chemical structure. More recent classifications are based on similarity of the carbon skeleton or the biochemical precursor. However, due their diversity the classification of alkaloids is sometimes still uncertain. The picture shows the structure formula of caffeine and its metabolic modifications

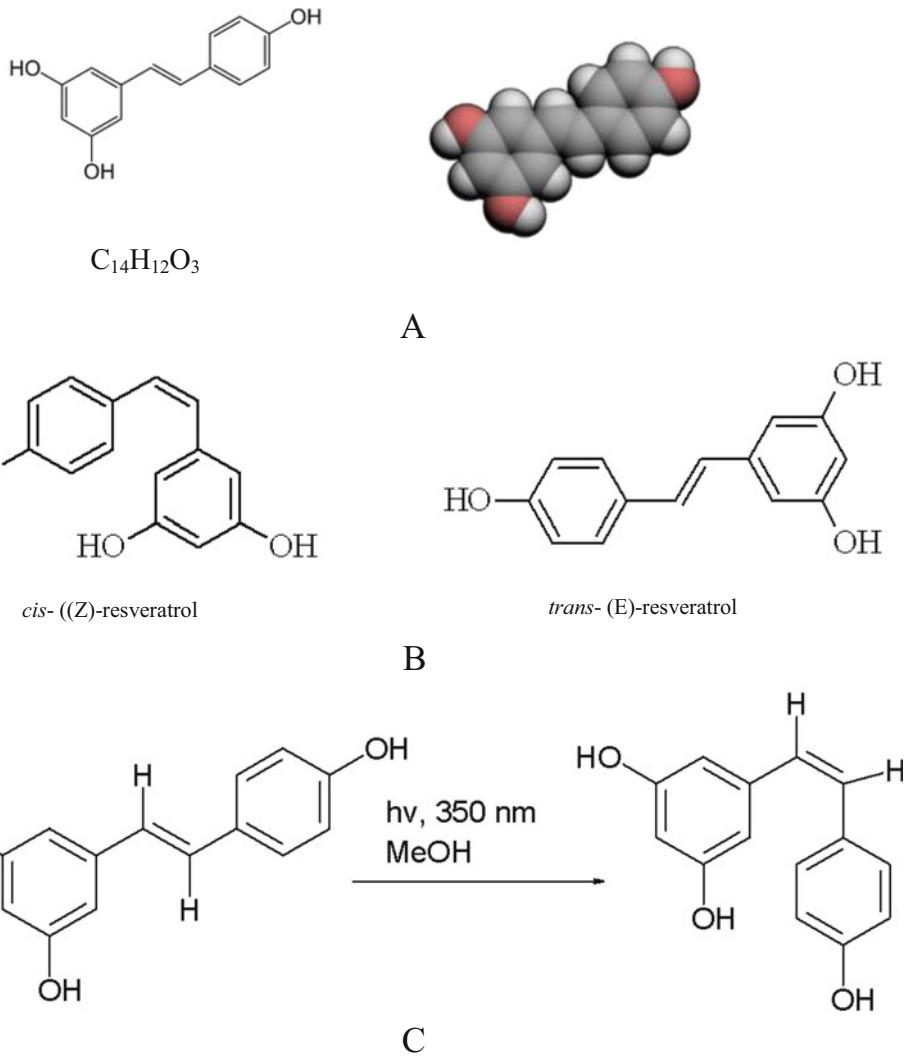

Fig. 2 (**a**) Empirical and structure formulas of *cis*-resveratrol (left and right, respectively). The number of C, H, and O atoms is also given. (**b**) Structure formula of *cis*- and *trans*-resveratrol (left and right, respectively). (**c**) Transition of resveratrol into the two known isomers mediated by UV light

with modifications from: Soleas et al. 1997; Schröder 1999; Jeandet et al. 2002, Cichewicz and Kouzi 2002).

2.3 Occurrence in Nature

Resveratrol was originally found in the berries of the wine grape (*Vitis vinifera*), but it is also present in the roots, seeds, and stock of the plant. The highest concentration is found in the peel of the berries although the content may vary significantly depending upon the fruit source from which resveratrol is extracted and upon the way the fruit is processed. Red wine contains a relevant amount of RV, but it can be also obtained from diverse sources like pea- and pine nuts as well as mulberries: actually the compound can be isolated from all intensely pigmented fruits (Table 1 shows the amount of RV present in various foods and beverages). In any case, this natural product is known since centuries and was used in the Japanese and Chinese traditional medicine: actually, RV was obtained in its crude original form, from the desiccated roots of the Japanese knotweed (*Polygonum cuspidatum*) where is present at a 400-fold higher concentration as compared to grapes or red wine (Fig. 4).

3 Relevant Biological Actions

3.1 Antitumor Activity in Mammals

The main feature of a transformed tumor cell is represented by its unregulated proliferation that determines a significantly increase in duplicative speed as compared to normal tissue cells. There are a number of reasons accounting for this metabolic dysregulation, essentially loss of control of the cell cycle and/or evasion from the apoptotic death mechanisms which represent the principal mode to control differentiation and size of the cell population. With respect to this, cyclins constitute a

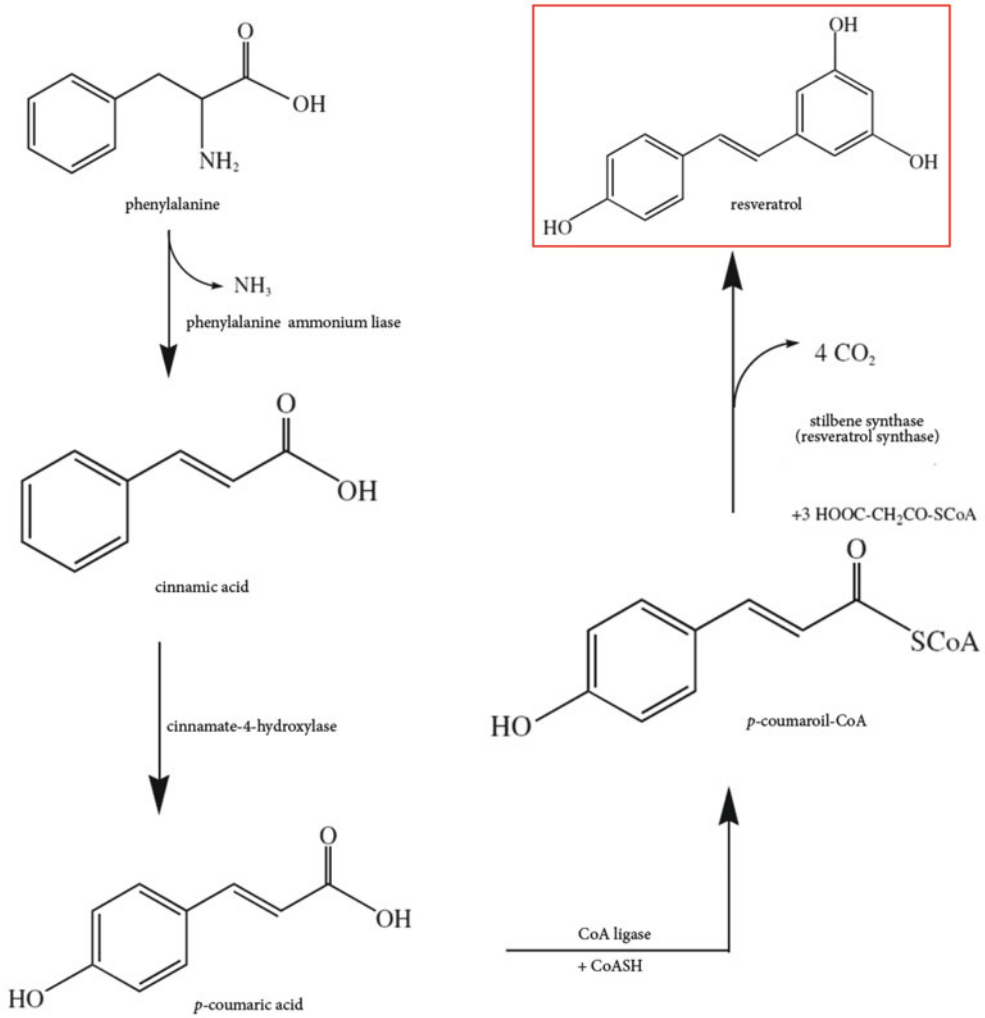

Fig. 3 Schematic illustration of the RV chemical biosynthesis of *Vitis vinifera*. See text for details

Table 1 Resveratrol content in various commercially available commodities

Food	Total resveratrol (mg/100 gm)	Beverages and seasonings	Resveratrol (mg/100 mL)	
			Mean	Range
Peanuts	0.08	Red wine	0.27	0–2.78
Peanut, roasted	0.06	Rosé wine	0.12	5.00×10^{-3} to 0.29
Peanut butter	0.04	White wine	0.04	0.00–0.17
Red grapes	0.24–1.25[a]	Sparkling wine	9.00×10^{-3}	8.00×10^{-3} to 1.00×10^{-2}
Cocoa powder	0.14–0.23[a]	Green grape juice	5.08×10^{-3}	0.00 to 1.00×10^{-2}
Cocoa–chocolate (dark)	0.04[a]	Vinegar	6.86×10^{-3}	0.02–7.75
Pistachio, dehulled	0.11			
Lingonberry, raw	3.00			
Red currant, raw	1.57			
Strawberry, raw	0.35			

Re-elaborated from stilbenes resveratrol in foods and beverages. Phenol-Explorer 2016. Link: http://phenol-explorer.eu/contents/polyphenol/592

[a]These values may vary according to the cultivar of red grapes, the hydration of the powder (cocoa), or its percentage (w/w) in the finished product (chocolate). The same applies to wines and seasonings. Furthermore, the RV content in wine is different from that of grapes since its extraction from the fruit depends on the wine making and fermentation techniques (e.g., the duration of the contact time with the peels of the grape berries). Also, resveratrol in its 3-glucosidic form is hydrolyzed, thus yielding both *trans*- and *cis*-resveratrol. Data for soy sauce and other oriental seasonings as well traditional foods like kosher pickles are not available. Traces of resveratrol and other lycopenes, on the other hand, are present in cosmetics, but the skin adsorption of these compounds deserves further assessment

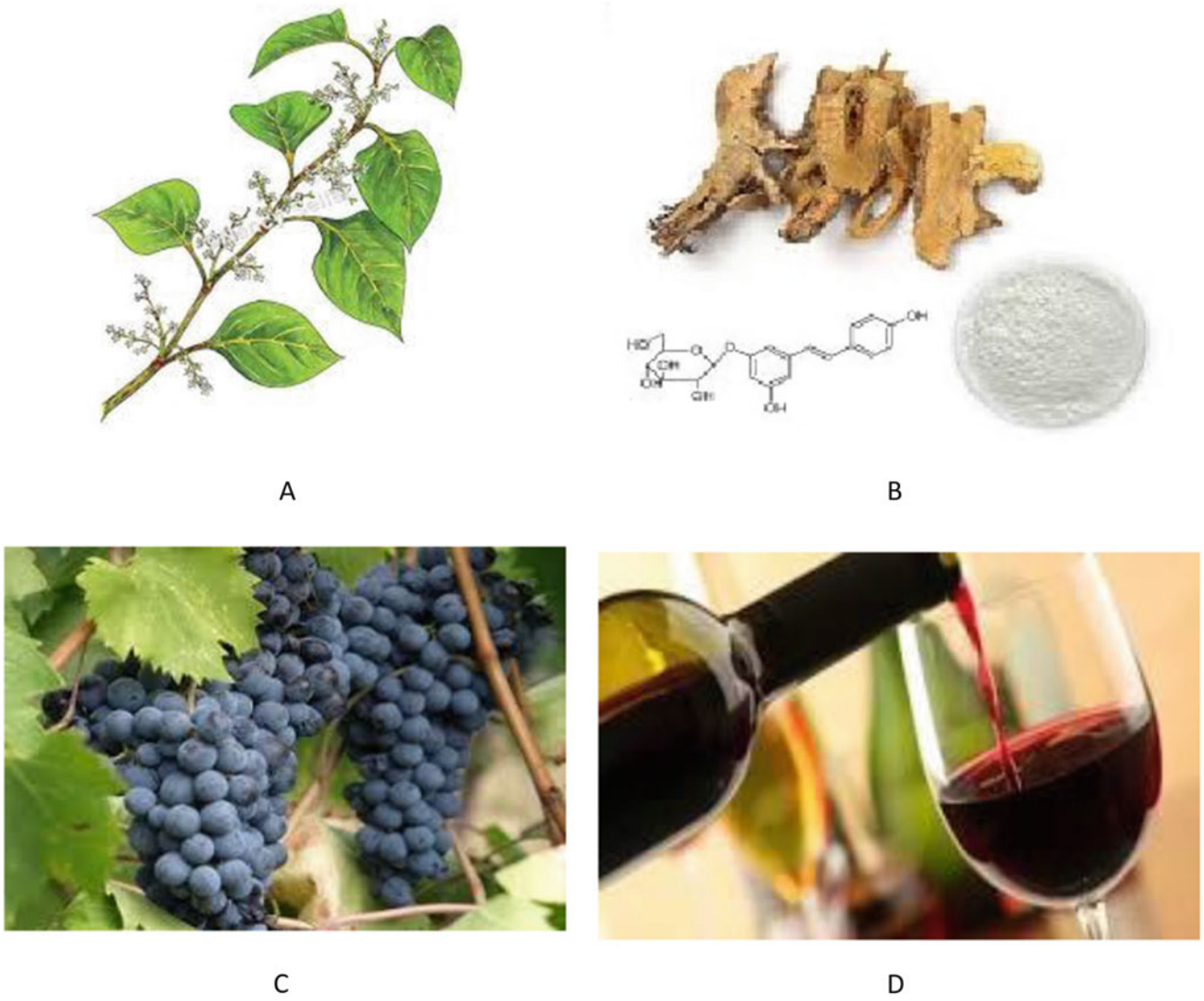

Fig. 4 Top panels. (**a**) Graphic representation of the plant *Polygonum cuspidatum* also known as *Fallopia japonica*. (**b**) Desiccated roots of the plant; *trans*-resveratrol chemical formula; final commercially available powder. (**c**) Bunches of wine blue grapes. (**d**) The final product, red wine. Due to its high content of resveratrol, the moderate assumption of red wine is considered beneficial (the French paradox). However, it should be borne in mind that the "liberal" usage of alcoholic beverages is highly detrimental for the psychophysical human conditions

family of protein factors able to regulate the correct execution and completion of the cell cycle: if the block in G1 phase takes place, the apoptotic pathway is activated. This phenomenon was observed, for instance, in the human epidermal carcinoma (Ahmad et al. 2001), and somewhat more recent data demonstrated the hindrance of progression toward the S phase (Liao et al. 2010). With respect to this, RV has been shown to modulate the cdk-cyclin-dependent mechanisms. This drug has been also involved in the development of the human colon-rectal since it induces clustering of the Fas ligand and its redistribution in sphingolipid matrix of the transformed cells which, in turn, is associated with the formation of DISC (death-inducing signaling complex; Delmas et al. 2011). Studies in a mouse model of epidermal tumor in mammary glands demonstrate that RV counteracts tumorigenesis. Resveratrol also increases the antitumor activity of the mTOR inhibitors, and finally, it represses the activation pathway of tumor-stimulating factors in mammary tumor cell lines (He et al. 2011). The gene product nf-kb is involved in the regulation of a vast number of protein factors modulating very complex biological phenomena such as inflammation, cell proliferation, and carcinogenesis: it has been suggested that RV inhibits the action of this factor (Singh et al. 2011). An interesting consideration, not directly associated to the antitumor property of RV, is that this compound is also a regulator of the human SIRT-1 gene which encodes a protein involved in aging and is considered as a potential factor of longevity (Signorelli and Ghidoni 2005; Singh et al. 2011). However, as of 2018, the evidence that resveratrol has life-prolonging properties in humans remains a matter of debate. Furthermore, the limited

bioavailability of resveratrol may further impede its potential effects (Pallauf et al. 2016; Wahl et al. 2018. See also the section on RV pharmacology in this chapter).

3.2 Antioxidant Properties

The main causative agent of atherosclerosis, and chronic artery inflammation, depends both on the individual lifestyle and environmental conditions. Therefore, tobacco smoking, pollution, hypercholesterolemia, hypertension, and other conditions (e.g., diabetes and obesity) are at the basis of cardiac/coronary problems. One of the final stages in the complex genesis of atherosclerosis is the damage of the vasal endothelium, the deposit of the low-density lipid fraction (LDL) and, finally, the aggregation of platelets. Resveratrol may play a protective role due to its very high antioxidant character (Matos et al. 2012): for instance, treatment of bovine aorta cells with RV delays the formation of the atheroma. Parallel treatment with mitosis-stimulating factors such as PDGF may act synergistically with RV (Araim et al. 2002).

Lipids containing unsaturated fatty acids, or their esters, are oxidized by the molecular oxygen present in cells; lipid peroxidation is a direct consequence of the formation of free reactive oxygen species (ROS). Resveratrol can inhibit the oxidation of the low-density lipid (LDL) fraction circulating in the blood. This oxidation is a primary event in the development of atherosclerosis: the strong antioxidant character of RV attenuates the formation of ROS and, consequently, the cytotoxicity induced by LDL peroxidation as well as the accumulation of intracellular calcium which is also an effect induced by the drug. The final result is the inhibition of caspase-3, an enzyme playing a crucial role in the execution of apoptosis (Shalini et al. 2015). It should be considered that high levels of ROS stimulate platelet aggregation: also in this case, the antioxidant action of the drug and its ability to reduce platelet adhesion to the type I collagen enable *trans*-resveratrol to limit this phenomenon. This ends in an impairment of blood coagulation and establishment of the atherosclerotic process (Zbikowska et al. 1999).

3.3 Cell Death

The strong antioxidant activity of RV with consequent protection from cell damage, as repeatedly stated above, is common knowledge; however the drug may also paradoxically induce apoptosis and autophagy (Kou and Chen 2017). These effects, monitored in a time- and concentration-dependent mode, were demonstrated in different models of cell cultures (Berardi et al. 2009; Whitlock and Baek 2012; Aluyen et al. 2012; Hasima and Ozpolat 2014). Cytofluorimetric analysis also showed activation of the apoptotic marker factors and the occurrence of typical apoptotic morpho-functional alterations (Zhang et al. 2011). In any case the preferential target of RV seems to be represented by the transformed cells (Berardi et al. 2009; Zhang et al. 2012; Risuleo 2016). As far as the cell cycle is concerned, RV can induce an arrest in S phase in murine pre-adipocytes and a significant increase of the intracellular concentration of lactic dehydrogenase (LDH): a hallmark of apoptosis. However the paradoxical effects of the drug which can protect the cell or vice versa induce its death, and its synergistic effects with diverse antioxidant, are a clear sign of the complex interactions of the drug with the target cells. A number of studies demonstrated that this behavior is shared by other natural products (see for instance: De la Lastra and Villegas 2007; Ricci et al. 2009; Chen et al. 2011; Ullah et al. 2015; Wang et al. 2012).

3.4 Antiviral Activity

The first evidence of the antiviral action of RV dates back to 1999 when the inhibition of the replication of herpes simplex virus (HSV) was published (Docherty et al. 1999). Also, its improving effects in a mouse model system of vaginal infection were also shown (Docherty et al. 2005). Subsequently the same authors demonstrated the RV-dependent inhibition of varicella-zoster DNA replication in a human fibroblast cell line. This action is exerted in the early phases of the infection mainly at the level viral mRNA transcription (Docherty et al. 2006). Later studies, however, ascribed this indirect antiviral action to the inhibition by RV of the formation of the NF-kb dimeric complex, an essential prerequisite for DNA synthesis (Gregory et al. 2004); an analogous phenomenon occurs in the case of influenza A virus where the proteins necessary for the assembly and maturation of the viral capsid, after cytoplasmic synthesis, are not efficiently transported to the nucleus (Palamara et al. 2005). Relatively recent work suggested a possible role of RV in the control of the complications after the infection by the H1N1 virus. As reviewed by Uchide and Toyoda, this negative control would be due to the RV-mediated neutralization of the superoxide anion produced by macrophages which would limit the consequences of the viral infection. Resveratrol has also been suggested to influence negatively the vitality of lymphoma cells infected with the Epstein-Barr virus (De Leo et al. 2012) which is involved in different human pathologies (Tooze 1981).

It has been suggested that RV may also have a role in the control of the HIV infection in humans since it potentiates the action of antiviral agents used in anti-HIV therapy; however due to the extremely complicated pathological picture of AIDS, in the opinion of the authors of this chapter, this observation deserves further and deeper evaluation. Finally, in our laboratory, we explored the action of RV on the murine

polyomavirus (Py) replication. Also in this case, RV has shown strong antiviral properties since it reduces the viral DNA synthesis both in murine fibroblasts and in human promyelocytic leukemia cells. The inhibition occurs at low non-cytotoxic doses of the drug which does not seem to impede viral adsorption and entry into the cell. These data combined with other observations from our laboratory on another natural substance strongly suggest that the cell membrane is the main target of RV (Ricci et al. 2009; Aiello et al. 2011). In particular, the role of the membrane permeability with respect to the RV bioactivity will be discussed in further detail in the following section.

3.5 Resveratrol and the Cell Membrane

What discussed previously opens new questions about the mode of action of RV in particular: How does the drug find its target(s)? Is the multifaceted "therapeutic" efficacy also mediated by binding molecular carriers which improve the penetration across the cell membrane and stabilize its intracellular "survival?" Finally, is it possible to construct "cargo" vehicles able to deliver to right cell district thus improving its efficacy? This aspect, in particular, will be the subject of another chapter.

In any case, albumin could act as a good transporter since this protein is able to bind amphiphilic molecules, and in addition to RV, it interacts with other natural substances such as genistein and curcumin (Bourassa 2010). Studies indicate that RV is able to bind one of the major human plasma proteins (HAS). However, the amount of bound drug is inversely proportional to its plasma concentration which makes this result of very difficult interpretation (Jiang 2008). The entry of RV has been suggested to occur through a clathrin-independent process of endocytosis; but lipid rafts seem to play a role since agents that damage their functionality also inhibit penetration of the drug within the cell (Colin et al. 2011). We investigated the mechanism of RV entry into the cell by electrorotation: a biophysical approach which was amply discussed and reviewed (Bonincontro and Risuleo 2015). By this experimental strategy, we were able to evaluate the cell membrane function and intrinsic role in mediating the action of RV. Result from our laboratory demonstrates that the drug is promptly uptaken by the cell population which is not blocked in G1 at a relevant extent (Berardi et al. 2009; Bonincontro et al. 2018).

For a more detailed review on the various and diversified biological properties of resveratrol, the reader should address a previously published work (Risuleo 2016). Table 2 reports a synopsis of the different bioactivities of the drug and the related reference data.

Table 2 Activities/properties exhibited by resveratrol

Action/role	System (s)[a]	Reference/s
Aging	AMS, HS	(Sarubbo et al. 2017; McCubrey et al. 2017)
Autophagy/ cell death	CCS, AMS	(Owen et al. 2017; Tsai et al. 2017; Bhat et al. 2018; Cao et al. 2018; Fan et al. 2018)
Brain	HS, AMS	(Castro et al. 2017; Amro et al. 2018; Lange and Li 2018; Lee et al. 2018)
Cancer	CCS, AMS	(Crooker et al. 2018; Elshaer et al. 2018; Espinoza et al. 2018; Huminiecki and Horbańczuk 2018; Perez-Vizcaino and Fraga 2018; Zhai et al. 2018)
Cardiovascular	AMS, HS/CT	(Treviño-Saldaña and García-Rivas 2017; Bird et al. 2015)
Diabetes	AMS, HS/CT	(Oliveira et al. 2017; Zhu et al. 2017; Popescu et al. 2018)
Skin	HS/CT	(Farris et al. 2013; Ganesan and Choi 2016; Chedea et al. 2011)

These features of the drug are additional to those examined in extenso in the text

[a]Acronyms: AMS, animal model systems; CCS, cell culture systems; HS/CT, human systems/clinical trials

4 Pharmacological Aspects: Pharmacodynamics and Pharmacokinetics

Resveratrol has been identified as a pan-assay interference compound, which produces positive results in many different laboratory assays. The pan-assay-defined compounds may produce false positives, especially in high-throughput screenings, since they tend to react in a nonspecific manner with numerous biological targets within the cell, rather than affecting a specific one (Baell and Walters 2014). Therefore some caution is necessary when analyzing the ample spectrum of actions inhibited by RV. One of the ways to rationalize the multi-target effect of this natural product takes into account its ability to interact with the cell membrane which could cause a cascade of effects in other districts of the cell not directly involved with the membranes (Ingólfsson et al. 2014; Bonincontro and Risuleo 2015, Vang 2015; see also references on this matter reported above in the section: "Resveratrol and the cell membrane"). As a matter of fact, many and very diverse specific biological targets of resveratrol, e.g., hormone receptors, apoptotic factors, and cell cycle regulators, have been identified (Vang 2015). The cell membrane allows the cytoplasm matrix to communicate with the outer world and acts as a highly selective filter. Biological membranes participate to a number of transport mechanisms such as passive osmosis and diffusion. Therefore, their

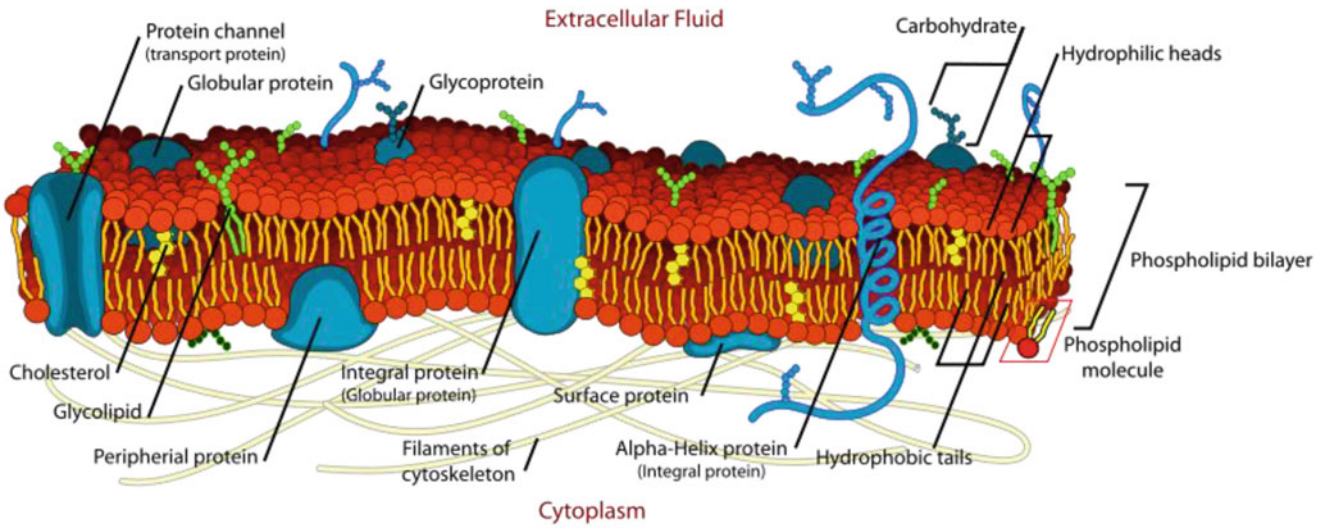

Fig. 5 The cartoon depicts the structure of a typical cell membrane. Its involvement in numerous cell functions and activities is clearly illustrated. The image is freely available on the net and not covered by copyright. We report here the www-link: https://en.wikipedia.org/wiki/Cell_membrane#mediaviewer/File:Cell_membrane_detailed_diagramen.svg. The work of the author of this picture, Lady of Hats, is acknowledged

integrity plays a fundamental role in a number of cell functions such as metabolism, maintenance of the basal homeostasis, and, although in an indirect manner, cell differentiation and development. Recently, it has become clear the role of the cell membrane in "filtering" the paracrine apoptogenic and/or intrinsic death signals; therefore, any agent affecting the efficient function of the cell membrane could play a binary role: helping cell survival and correct proliferation or vice versa triggering mechanisms leading to damage; for a relatively recent review, see Mattetti and Risuleo (2014) and references therein. The complexity and function multiplicity of the cell membrane are depicted in Fig. 5.

Other studies conducted in vitro indicate that resveratrol activates sirtuins. These proteins influence a wide variety of cellular processes such as aging, transcription, apoptosis, inflammation, and stress resistance, as well as energy efficiency and alertness during energy situations such as low-calorie diets. Finally, resveratrol seems to stimulate the production of superoxide dismutase (SOD-2) and GPER activity. This latter is a G protein that in humans interacts with the estrogen receptor-1 GPER and is activated by the female sex hormone. Resveratrol was shown to act in vitro, as an agonist of peroxisome proliferator-activated receptor gamma, a nuclear receptor under pharmacological research as a potential agent for the treatment of type 2 diabetes (Yang et al. 2015).

One way of administering resveratrol in humans is buccal delivery without swallowing, that is, by direct absorption through tissues inside the mouth. One milligram of resveratrol in solution (50% alcohol/water) retained in the mouth for 1 min can be monitored 2 min later in the plasma at concentration of 37 ng/mL (free resveratrol). This same concentration of non-modified native RV is reached after administration of 250 mg of the drug in a pill form (Asensi et al. 2002). However, the relatively low solubility of RV in water limits the amount that can be absorbed through the buccal mucosa. Therefore the viability of the buccal delivery method is questionable due to the relatively low aqueous solubility of the molecule. Therefore further assessment of the efficacy of RV buccal delivery for RV is required (Madhav et al. 2009; Ansari et al. 2011).

According to pharmacological evaluations, about 70% of resveratrol is absorbed after oral administration; however its oral bioavailability is approximately 0.5% due to extensive chemical modifications, such as glucuronidation and sulfation, undergone by the drug: these occur at liver level (Walle 2011). Finally, the production of the RV proprietary formulation SRT-501 was discontinued by GlaxoSmithKline since "the company decided to terminate the Phase 2 trial of SRT501 in multiple myeloma and halt development of the drug as a potential myeloma treatment. The SRT501 formulation of resveratrol may only offer minimal efficacy, while increasing the chances of kidney failure."

See The Myeloma Beacon Staff. Nov 30, 2010 (https://myelomabeacon.org/news/2010/11/30/glaxosmithkline-halts-all-further-development-of-resveratrol-drug-srt501/).

Resveratrol was detected in cerebrospinal fluid in a human study involving oral administration of 500 mg over 13 weeks, (Turner et al. 2015) which suggests that the drug is able to cross the blood-cerebrospinal fluid barrier. Resveratrol is also extensively metabolized in the liver and lungs which are the major sites of its metabolic transformations (Sharan and Nagar 2013).

5 Adverse Effects

A limited number of human studies have shown that resveratrol is generally well-tolerated. Clinical trials showed that one person taking a 1000 mg daily dose developed an itchy rash that was resolved after discontinuation; in the same study, also the blood pressure seemed to be affected. In four of the published trials, people had increased frequency of bowel movements and loose stools in first month of the treatment. In a yearlong Phase 2 trial in people with Alzheimer's, the most frequent adverse effects were diarrhea, weight loss, and nausea (Hausenblas et al. 2014; Fogacci et al. 2018). All in all, these effects do seem to be very important if one considers the potential advantages deriving from the treatment with RV.

6 Concluding Remarks and Future Directions

Control of cell death and senescence seems to be the most relevant effects of the administration of resveratrol. This action is essentially exerted through the interaction of RV with the cell membrane. However, like other natural products, RV may give rise to paradoxical effects; therefore its use as a multi-target therapeutic means should be considered with some *caveats*. For instance, resveratrol is apparently able to cross the membrane without causing serious consequences for the cell viability and survival, but its limited water solubility and bioavailability may reduce the use of this natural substance for therapeutic purposes. This should urge the search for new ways to deliver the drug to the cell population or to the cell district where it may play its role to contrast and/or eliminate pathological phenomena. In any case, the usage of this, as well as other medicaments of natural origin, should be done only after an accurate evaluation of their biocompatibility even though resveratrol does not seem to show significant adverse effects. With respect to the pharmacological use of RV, nanotechnologies may be of great support for an efficient and biocompatible application for the resolution of health problems. As a matter of fact, delivery mediated by nanoparticles such as liposomes, vesicles, or nanotubes may represent the new way for a safe and efficient way to dispatch molecules endowed of therapeutic capacities.

References

Ahmad N, Adhami VM, Afaq F et al (2001) Resveratrol causes WAF-1/p21-mediated G(1)-phase arrest of cell cycle and induction of apoptosis in human epidermoid carcinoma A431 cells. Clin Cancer Res 7:1466–1473

Ahuja I, Kissen R, Bones AM (2012) Phytoalexins in defense against pathogens. Trends Plant Sci 17:73–90

Aiello C, Berardi V, Ricci F, Risuleo G (2011) Biological properties of a methanolic extract of neem oil, a natural oil from the seeds of the Neem tree (*Azadirachta indica* var. A. Juss). In: Preedy VR, Watson RR, Patel VB (eds) Nuts & seeds in health and disease prevention, 1st edn. Academic Press is an imprint of Elsevier, London, Burlington, San Diego, pp 813–821. ISBN: 978-0-12-375688-6

Aluyen JK, Ton QN, Tran T et al (2012) Resveratrol: potential as anticancer agent. J Diet Suppl 9(1):45–56

Amro MS, Teoh SL, Norzana AG et al (2018) The potential role of herbal products in the treatment of Parkinson's disease. Clin Ter 169 (1):e23–e33

Ansari KA, Vavia PR, Trotta F et al (2011) Cyclodextrin-based nanosponges for delivery of resveratrol: in vitro characterisation, stability, cytotoxicity and permeation study. AAPS Pharm Sci Technol 12(1):279–286

Araim O, Ballantyne J, Waterhouse AL et al (2002) Inhibition of vascular smooth muscle cell proliferation with red wine and red wine polyphenols. J Vasc Surg 35(6):1226–1232

Asensi M, Medina I, Ortega A et al (2002) Inhibition of cancer growth by resveratrol is related to its low bioavailability. Free Radic Biol Med 33(3):387–398

Baell J, Walters MA (2014) Chemistry: chemical con artists foil drug discovery. Nature 513:481–483

Berardi V, Ricci F, Castelli M, Galati G, Risuleo G (2009) Resveratrol exhibits a strong cytotoxic activity in cultured cells and has an antiviral action against polyomavirus: potential clinical use. J Exp Clin Cancer Res 28:96–105

Bhat P, Kriel J, Shubha Priya B et al (2018) Modulating autophagy in cancer therapy: advancements and challenges for cancer cell death sensitization. Biochem Pharmacol 147:170–182

Bird JK, Raederstorff D, Weber P et al (2015) Cardiovascular and antiobesity effects of resveratrol mediated through the gut microbiota. Adv Nutr 8:839–849

Bonincontro A, Risuleo G (2015) Electrorotation: a spectroscopic imaging approach to study the alterations of the cytoplasmic membrane. Adv Mol Imaging 5:1–15

Bonincontro A, Domenici F, Milardi GL, Risuleo G (2018) Differential dielectric behavior of the plasma membrane in mouse fibroblasts and human embryo kidney cells. Intl J Sci Res 7:68–71

Bourassa P (2010) Resveratrol, genistein, and curcumin bind bovine serum albumin. J Phys Chem 114:3348–3354

Burow M, Halkier BA (2017) How does a plant orchestrate defense in time and space? Using glucosinolates in *Arabidopsis* as case study. Curr Opin Plant Biol 38:142–147

Cao W, Dou Y, Li A (2018) Resveratrol boosts cognitive function by targeting SIRT1. Neurochem Res 43(9):1705–1713. https://doi.org/10.1007/s11064-018-2586-8

Castro OW, Upadhya D, Kodali M et al (2017) Resveratrol for easing status epilepticus induced brain injury, inflammation, epileptogenesis, and cognitive and memory dysfunction-are we there yet? Front Neurol 13(8):603

Chedea VS, Vicaş SI, Sticozzi C et al (2011) Resveratrol: from diet to topical usage. Food Funct 8:3879–3892

Chen S, Xiao X, Feng X et al (2011) Resveratrol induces Sirt1-dependent apoptosis in 3T3-L1 preadipocytes by activating AMPK and suppressing AKT activity and survivin expression. J Nutr Biochem 23(9):1100–1112

Cho MH, Lee SW (2015) Phenolic phytoalexins in rice: biological functions and biosynthesis. Int J Mol Sci 16(12):29120–29133

Cichewicz RH, Kouzi ESA (2002) Resveratrol oligomers: structure, chemistry, and biological activity. In: Atta-ur-Rahman (ed) Studies in natural products chemistry, vol 26. Elsevier, Amsterdam, pp 507–579

Colin D, Limagne E, Jeanningros-Arnaud S et al (2011) Endocytosis of resveratrol via lipid rafts and activation of downstream signaling pathways in cancer cells. Cancer Prev Res (Phila) 4(7):1095–1106. https://doi.org/10.1158/1940-6207.CAPR-10-0274

Crooker K, Aliani R, Ananth M (2018) A review of promising natural chemopreventive agents for head and neck cancer. Cancer Prev Res (Phila) 11(8):441–450. https://doi.org/10.1158/1940-6207.CAPR-17-0419

De la Lastra CA, Villegas I (2007) Resveratrol as an antioxidant and pro-oxidant agent: mechanisms and clinical implications. Biochem Soc Trans 35(5):1156–1160

De Leo A, Arena G, Lacanna E et al (2012) Resveratrol inhibits Epstein Barr Virus lytic cycle in Burkitt's lymphoma cells by affecting multiple molecular targets. Antivir Res 96(2):196–202

Delmas D, Solary E, Latruffe N (2011) Resveratrol, a phytochemical inducer of multiple cell death pathways: apoptosis, autophagy and mitotic catastrophe. Curr Med Chem 18(8):1100–1121

Dixon RA, Paiva NL (1995) Stress-induced phenylpropanoid metabolism. Plant Cell 7:1085–1097

Docherty JJ, Fu MM, Stiffler BS et al (1999) Resveratrol inhibition of herpes simplex virus replication. Antivir Res 43:145–155

Docherty JJ, Fu MM, Hah JM et al (2005) Effect of resveratrol on herpes simplex virus vaginal infection in the mouse. Antivir Res 67:155–162

Docherty JJ, Sweet TJ, Bailey E et al (2006) Resveratrol inhibition of varicella-zoster virus replication in vitro. Antivir Res 72:171–177

Echeverri F, Torres F, Quinones W et al (1997) Danielone, a phytoalexin from papaya fruit. Phytochemistry 44(2):255–256

Elshaer M, Chen Y, Wang XJ et al (2018) Resveratrol: an overview of its anti-cancer mechanisms. Life Sci 207:340–349

Espinoza JL, Kurokawa Y, Takami A (2018) Rationale for assessing the therapeutic potential of resveratrol in hematological malignancies. Blood Rev S0268–960X(17):30124–30128

Fan Y, Chiu JF, Liu J (2018) Resveratrol induces autophagy-dependent apoptosis in HL-60 cells. BMC Cancer 18(1):581

Farris P, Krutmann J, Li YH (2013) Resveratrol: a unique antioxidant offering a multi-mechanistic approach for treating aging skin. J Drugs Dermatol 12(12):1389–1394

Favaron F, Lucchetta M et al (2009) The role of grape polyphenols on trans-resveratrol activity against *Botrytis cinerea* and of fungal laccase on the solubility of putative grape PR proteins. J Plant Pathol 91(3):579–588

Fogacci F, Tocci G, Presta V et al (2018) Effect of resveratrol on blood pressure: a systematic review and meta-analysis of randomized, controlled, clinical trials. Crit Rev Food Sci Nutr 58(2):1–14

Ganesan P, Choi DK (2016) Current application of phytocompound-based nanocosmeceuticals for beauty and skin therapy. Int J Nanomedicine 11:1987–2007

Glazebrook J, Ausbel FM (1994) Isolation of phytoalexin-deficient mutants of *Arabidopsis thaliana* and characterization of their interactions with bacterial pathogens. PNAS 91:8955–8959

Gregory D, Hargett D, Holmes D et al (2004) Efficient replication by herpes simplex virus type 1 involves activation of the IFkappaB kinase-IkappaB-p65 pathway. J Virol 78(24):13582–13590

Großkinsky DK, van der Graaff E, Roitsch T (2012) Phytoalexin transgenics in crop protection—fairy tale with a happy end? Plant Sci 195:54–70

Harborne JB (1999) The comparative biochemistry of phytoalexin induction in plants. Biochem Syst Ecol 27(4):335–367

Hart JH, Hillis WE (1974) Inhibition of wood-rotting fungi by stilbenes and other polyphenols in *Eucalyptus sideroxylon*. Phytopathology 64:939–948

Hasima N, Ozpolat B (2014) Regulation of autophagy by polyphenolic compounds as a potential therapeutic strategy for cancer. Cell Death Dis 5:e1509. https://doi.org/10.1038/cddis.2014.467

Hausenblas HA, Schoulda JA, Smoliga JM et al (2014) Resveratrol treatment as an adjunct to pharmacological management in type 2 diabetes mellitus-systematic review and meta-analysis. Mol Nutr Food Res 59(1):147–159

He X, Wang Y, Zhu J et al (2011) Resveratrol enhances the anti-tumor activity of the mTOR inhibitor rapamycin in multiple breast cancer cell lines mainly by suppressing rapamycin-induced AKT signaling. Cancer Lett 301(2):168–176

Huminiecki L, Horbańczuk J (2018) The functional genomic studies of resveratrol in respect to its anti-cancer effects. Biotechnol Adv 36 (6):1699–1708

Ingólfsson HI, Thakur P, Herold KF et al (2014) Phytochemicals perturb membranes and promiscuously alter protein function. ACS Chem Biol 9:1788–1798

Jeandet P, Douillet-Breuil AC, Bessis R et al (2002) Phytoalexins from the Vitaceae: biosynthesis, phytoalexin gene expression in transgenic plants, antifungal activity, and metabolism. J Agric Food Chem 50:2731–2741

Jiang J (2008) Design, synthesis and spectroscopic studies of resveratrol aliphatic acid ligands of human serum albumin. Bioorg Med Chem 16:6406–6414

Kou X, Chen N (2017) Resveratrol as a natural autophagy regulator for prevention and treatment of Alzheimer's disease. Nutrients 9(9): E927. https://doi.org/10.3390/nu9090927

Lamuela-Raventos RM, Romero-Perez AI, Waterhouse AL et al (1995) Direct HPLC analysis of *cis*- and *trans*-resveratrol and piceid isomers in Spanish red *Vitis vinifera* wines. J Agric Food Chem 43 (2):281–283

Lange KW, Li S (2018) Resveratrol, pterostilbene, and dementia. Biofactors 44(1):83–90

Lee RHC, Lee MHH, Wu CYC et al (2018) Cerebral ischemia and neuroregeneration. Neural Regen Res 13(3):373–385

Liao PC, Ng LT, Lin LT et al (2010) Resveratrol arrests cell cycle and induces apoptosis in human hepatocellular carcinoma Huh-7 cells. J Med Food 13(6):1

Madhav NV, Shakya AK, Shakya P et al (2009) Orotransmucosal drug delivery systems: a review. J Control Release 140(1):2–11

Matos RS, Baroncini LA, Précoma LB et al (2012) Resveratrol causes antiatherogenic effects in an animal model of atherosclerosis. Arq Bras Cardiol 98(2):136–142

Mattetti A, Risuleo G (2014) Apoptosis: a mode of cell death. Biochem Mol Biol 2:34–39

Mattivi F, Reniero F, Korhammer S (1995) Isolation, characterization, and evolution in red wine vinification of resveratrol monomers. J Agric Food Chem 43(7):1820–1823

McCubrey JA, Lertpiriyapong K, Steelman LS et al (2017) Effects of resveratrol, curcumin, berberine and other nutraceuticals on aging, cancer development, cancer stem cells and micro-RNAs. Aging (Albany NY) 9(6):1477–1536

Meyer J, Murray SL, Berger DK (2016) Signals that stop the rot: regulation of secondary metabolite defences in cereals. Physiol Mol Plant Pathol 94:156–166

Molnár J, Engi H, Hohmann J et al (2010) Reversal of multidrug resistance by natural substances from plants. Curr Top Med Chem 10(17):1757–1768

Oliveira MDM, Varanda CMR, Félix MRF (2016) Induced resistance during the interaction pathogen x plant and the use of resistance inducers. Phytochem Lett 15:152–158

Oliveira ALB, Monteiro VVS, Navegantes-Lima KC et al (2017) Resveratrol role in autoimmune disease-AMini-review. Nutrients 19: E1306

Owen HC, Appiah S, Hasan N et al (2017) Phytochemical modulation of apoptosis and autophagy: strategies to overcome chemoresistance in leukemic stem cells in the bone marrow microenvironment. Int Rev Neurobiol 135:249–278

Palamara AT, Nencioni L, Aquilano K et al (2005) Inhibition of influenza A virus replication by resveratrol. J Infect Dis 191:1719–1729

Pallauf K, Rimbach G, Rupp PM et al (2016) Resveratrol and lifespan in model organisms. Curr Med Chem 23(41):4639–4680

Perez-Vizcaino F, Fraga CG (2018) Research trends in flavonoids and health. Arch Biochem Biophys 646:107–112

Popescu M, Bogdan C, Pintea A et al (2018) Drug Des Devel Ther 12:1985–1996

Prokop J, Abrman P, Seligson AL et al (2006) Resveratrol and its glycon piceid are stable polyphenols. J Med Food 9(1):11–14

Ricci F, Berardi V, Risuleo G (2009) Differential cytotoxicity of MEX: a component of Neem oil whose action is exerted at the cell membrane level. Molecules 14:122–132

Risuleo G (2016) Resveratrol: multiple activities on the biological functionality of the cell. In: Gupta R (ed) Nutraceuticals: efficacy, safety and toxicity. Elsevier/Academic Press, Amsterdam, pp 453–464

Sanchez Maldonado AF, Schieber A, Gänzle MG (2015) Plant defence mechanisms and enzymatic transformation products and their potential applications in food preservation: advantages and limitations. Trends Food Sci Technol 46(1):49–59

Santos Silva M, Barbosa Monteiro Arraes F, de Araújo Campos M et al (2018) Potential biotechnological assets related to plant immunity modulation applicable in engineering disease-resistant crops. Plant Sci 270:72–84

Sarubbo F, Moranta D, Asensio VJ et al (2017) Effects of resveratrol and other polyphenols on the most common brain age-related diseases. Curr Med Chem 24(38):4245–4266

Schröder J (1999) Probing plant polyketide biosynthesis. Nat Struct Biol 6:714–716

Schröder G, Brown JW, Schröder J et al (1988) Molecular analysis of resveratrol synthase. cDNA, genomic clones and relationship with chalcone synthase. Eur J Biochem 172(1):161–169

Shalini S, Dorstyn L, Dawar S et al (2015) Old, new and emerging functions of caspases. Cell Death Differ 22:526–539

Sharan S, Nagar S (2013) Pulmonary metabolism of resveratrol: in vitro and in vivo evidence. Drug Metab Dispos 41(5):1163–1169

Shih C-H, Chu IK, Yip WK et al (2006) Differential expression of two flavonoid 3′-hydroxylase cDNAs involved in biosynthesis of anthocyanin pigments and 3-deoxyanthocyanidin phytoalexins in Sorghum. Plant Cell Physiol 47(10):1412–1419

Signorelli P, Ghidoni R (2005) Resveratrol as an anticancer nutrient: molecular basis, open questions and promises. J Nutr Biochem 16 (8):449–466

Singh NP, Singh UP, Hegde VL et al (2011) Resveratrol (*trans*-3,5,4-′-trihydroxystilbene) suppresses EL4 tumor growth by induction of apoptosis involving reciprocal regulation of SIRT1 and NF-κB. Mol Nutr Food Res 55(8):1207–1218

Soleas GJ, Diamandis EP, Goldberg DM (1997) Resveratrol: a molecule whose time has come? And gone? Clin Biochem 30:91–113

Thomma BP, Nelissen I, Eggermont K et al (1999) Deficiency in phytoalexin production causes enhanced susceptibility of *Arabidopsis thaliana* to the fungus *Alternaria brassicicola*. Plant J 19(2):163–171

Tooze J (ed) (1981) Molecular biology of tumor viruses: DNA tumor viruses part 2. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY

Treviño-Saldaña N, García-Rivas G (2017) Regulation of sirtuin-mediated protein deacetylation by cardioprotective phytochemicals. Oxidative Med Cell Longev:1750306. https://doi.org/10.1155/2017/1750306

Tsai HY, Ho CT, Chen YK (2017) Biological actions and molecular effects of resveratrol, pterostilbene, and 3′-hydroxypterostilbene. J Food Drug Anal 25(1):134–147

Turner RS, Thomas RG, Craft S et al (2015) A randomized, double-blind, placebo-controlled trial of resveratrol for Alzheimer disease. Neurology 85(16):1383–1391

Ullah MF, Bhat SH, Hussain E et al (2015) Ascorbic acid in cancer chemoprevention: translational perspectives and efficacy. Curr Drug Targets 13(14):1757–1771

Vang O (2015) Resveratrol: challenges in analyzing its biological effects. Ann N Y Acad Sci 1348:161–170

Wahl D, Bernier M, Simpson SJ et al (2018) Future directions of resveratrol research. Nutr Health Aging 4(4):287–290

Walle T (2011) Bioavailability of resveratrol. Ann N Y Acad Sci 1215:9–15

Wang Z, Li W, Meng X, Jia B (2012) Resveratrol induces gastric cancer cell apoptosis via reactive oxygen species, but independent of sirtuin1. Clin Exp Pharmacol Physiol 39(3):227–232

Whitlock NC, Baek SJ (2012) The anticancer effects of resveratrol: modulation of transcription factors. Nutr Cancer 64(4):493–502

Yang T, Li S, Zhang X et al (2015) Resveratrol, sirtuins, and viruses. J Rev Med Virol 25(6):431–445

Zbikowska HM, Olas B, Wachowicz B et al (1999) Response of blood platelets to resveratrol. Platelets 10:247–252

Zhai T, Li S, Hu W et al (2018) Potential micronutrients and phytochemicals against the pathogenesis of chronic obstructive pulmonary disease and lung cancer. Nutrients 10(7):E813. https://doi.org/10.3390/nu10070813

Zhang YH, Guo JG, Guo ZH et al (2011) Involvement of p38-p53 signal pathway in resveratrol-induced apoptosis in MCF-7 cells. Yao Xue Xue Bao 46(11):1332–1337

Zhang W, Wang X, Chen T (2012) Resveratrol induces apoptosis via a Bak-mediated intrinsic pathway in human lung adenocarcinoma cells. Cell Signal 24(5):1037–1046

Zhu X, Wu C, Qiu S et al (2017) Effects of resveratrol on glucose controland insulin sensitivity in subjects with type 2 diabetes: systematic review and meta-analysis. Nutr Metab (Lond) 14:60. https://doi.org/10.1186/s12986-017-0217-z