Chapter 9
Resveratrol and Immunomodulation

Mayela Govea Salas, Leticia A. Menchaca Castro, Rafael G. Aráujo, Sujey A. Niño Herrera, Anna Iliná, Roberto Arredondo Valdés, María del Carmen Rodríguez Salazar, Mónica L. Chávez González, E. Patricia Segura Ceniceros, and Cristóbal N. Aguilar González

Abstract Resveratrol is a stilbenoid polyphenolic molecule widely known for its biological properties, which is available in nature in various varieties of grapes, berries, and some plants. It has been shown to play an important role in the prevention and treatment of chronic diseases such as cancer, heart disease, metabolic, degenerative, autoimmune diseases, and even viral infections. One of the main mechanisms of action that it presents is linked to its antioxidant capacity as it is a strict polyphenol, which gives it the ability to stimulate an immune response in the host by regulating and differentiating immune cells, promoting the synthesis of specific proteins, activate apoptosis, stimulate the secretion of pro-inflammatory cytokines, and even modulate gene expression. These effects have favored the decrease in the progression of various inflammatory and degenerative diseases, thus demonstrating the immunomodulatory capacity of resveratrol on in vitro and in vivo models.

Keywords Resveratrol · Immunomodulation · Immunotherapy · Bioactive compound

9.1 Introduction

The use of products obtained from these natural sources such as food, plants, and beverages has made it possible to use various natural molecules that are present in sources as secondary metabolites mainly. There is a diverse variety of bioactive

M. G. Salas (✉) · A. Iliná · R. A. Valdés · M. L. Chávez González · E. P. S. Ceniceros
Nanobioscience Group, Autonomous University of Coahuila, Saltillo, Coahuila, Mexico

Food Research Department, Autonomous University of Coahuila, Saltillo, Coahuila, Mexico
e-mail: m.govea.salas@uadec.edu.mx

L. A. Menchaca Castro · S. A. Niño Herrera
Nanobioscience Group, Autonomous University of Coahuila, Saltillo, Coahuila, Mexico

R. G. Aráujo · M. del Carmen Rodríguez Salazar · C. N. Aguilar González
Food Research Department, Autonomous University of Coahuila, Saltillo, Coahuila, Mexico

R. K. Kesharwani et al. (eds.), *Nutraceuticals and Functional Foods as Immunomodulators*, https://doi.org/10.1007/978-981-19-2507-8_9

molecules of natural origin and that can be extracted by various physical and chemical processes that are friendly to the environment, which can be purified and characterized for use in various areas of research (Kesharwani and Misra 2010; Keservani et al. 2017). An example of this is resveratrol, a molecule that has been discovered for several years and has been purified and studied in various cell models in vitro and in vivo, the number of investigations that generate contributions of the effects of resveratrol on various pathologies increases. Resveratrol is a polyphenol of natural origin that is found in various varieties of grapes and red berries; therefore, beverages and foods prepared from these fruits are rich in this polyphenol. Its structure is complex and has several structural varieties that are mentioned below.

Several studies with resveratrol have shown that it has various biological properties against various pathologies such as metabolic, cardiac, degenerative, inflammatory, and cancer diseases and even in various viral and microbial infections. The effects generated by resveratrol in these pathologies are attributed mainly by its antioxidant properties, because the mechanism of action of this compound occurs through immunomodulation processes, which allow the activation of various immunological pathways and cells of the immune system so that they can fight disease, or even promote the death of damaged or diseased cells, as well as the activation of metabolic, cellular, and molecular processes linked to cellular oxidative stress.

This immunomodulatory effect has been widely used in the studies and developments of immunotherapies, since modifications of immune responses can be used in various pathologies through the activation, attenuation, or induction of immunological effects for therapeutic purposes. In the development of this chapter, different biological activities related to the immunomodulatory effect of resveratrol will be addressed on different in vitro and in vivo study models, elucidating the signaling pathways, metabolism, and molecular processes related to resveratrol and its effect at the cellular and molecular level, confirming that it is one of the nutraceuticals with the highest number of therapeutic effects attributed to its structural properties.

9.2 Structure and Characteristics of Resveratrol

Resveratrol, also known as trans-resveratrol, is a hydroxylated stilbene derivative with two phenolic rings. IUPAC nomenclature is 5-[(E)-2-(4-hydroxyphenyl) ethenyl]benzene-1,3-diol. Being a stilbenoid compound, it is considered as an aromatic lipidic polycide molecule. It presents a condensed chemical formula of $C_{14}H_{12}0_3$ equivalent to 228.25 g/mol. This compound was first described in the 1940s when it was isolated from the plant *Veratrum grandiflorum* (Gambini et al. 2013). There are two isomers of this compound, *cis* and *trans*-resveratrol. The *trans* isomer is the most stable form and the one commonly found in nature. Resveratrol is considered a phytoalexin, because it is present in a wide variety of plant materials and has been shown to be toxic to a wide variety of microorganisms.

In nature, it can be found as a glycosylated compound in fruits such as berries, grosella, and peanuts (Catalogna et al. 2019). Another food with a higher resveratrol

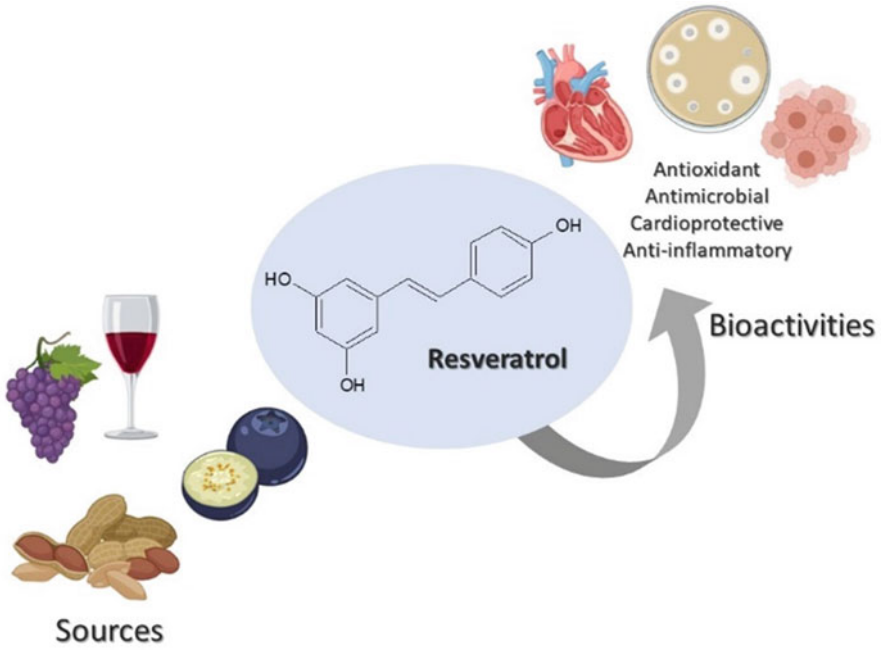

Fig. 9.1 Chemical structure of resveratrol, natural sources, and some bioactivities associated

content is grapes, and therefore, products derived from this fruit have a considerable amount of resveratrol such as juices and wines.

This polyphenol presents interesting biological activities, the most important being that of being a powerful antioxidant; another of the bioactivities shown is that of being an excellent antimicrobial, and tests have been carried out to combat cancer; it presents cardioprotective properties and helps in the reduction of inflammatory processes, anti-aging, and anti-diabetes and promotes neuroprotection (Moshawih et al. 2019; Raskovic et al. 2019) (Fig. 9.1).

9.3 Sources/Production and Applications in Health

Resveratrol RESV (trans-3,4,5-trihydroxystilbene) is a natural polyphenolic phytoalexin composed of two phenyl rings linked by a double bond, produced by plants in response to stress, and belongs to the group of phytoestrogens, it is attributed antioxidant and enzyme inhibition functions (cyclooxygenase, lipoxygenase and xanthine). In nature, it can be found in two isoforms, trans-resveratrol and cis-resveratrol, where the former is the most stable form found mainly in grape skins and red wine (Thapa et al. 2019).

Resveratrol is a powerful antioxidant, a natural polyphenol produced by more than 70 species of plants in response to stressful situations (ultraviolet radiation, fungal infections, etc.) (Thapa et al. 2019); it is present in several fruits that are part of the human diet, such as blueberries (*Vaccinium* spp.), currant, blackberries (*Morus* spp.), peanuts (*Arachis hypogaea*), as well as red wine which is the one that provides the highest content of this (Borge et al. 2013; Salehi et al. 2018). Extracting resveratrol in commercial quantities is difficult due to its low concentration and several extraction and purification steps, which is harmful to the environment. However, it has been extracted from the wild root of *Polygonum cuspidatum*, grape skins and seeds, and the domestic giant knotweed from China, the world's leading producer. To obtain resveratrol, alternative methods are needed as it has a high medicinal and dietary value. However, a high amount of resveratrol can be produced by chemical synthesis, with the formation of unwanted by-products that contaminate the resveratrol and make its purification difficult (Salehi et al. 2018).

Resveratrol has a wide range of biological activities such as anti-inflammatory, antiviral, and antitumor properties (rats). Proposed anticancer mechanisms for resveratrol include (a) inhibition of ribonucleotide reductase, DNA polymerase, protein kinase C, or cyclooxygenase-2 activities, (b) inhibition of cell proliferation and free radical-induced carcinogenesis, and (c) induction of apoptosis (Vélez-Marín et al. 2012). Resveratrol eliminates free radicals, such as reactive oxygen species and reactive nitrogen species, produced by the metabolism of the body, minimizes radical damage to delicate organs, inhibits lipid peroxidation, and increases cholesterol in the blood, which improves neurological and cardiovascular activities (Table 9.1) (Kuršvietienė et al. 2016).

Resveratrol is rapidly absorbed, metabolized by glucuronides or sulfate conjugates, and distributed to various organs. In general, polyphenol metabolites are rapidly eliminated from plasma, which indicates that a daily consumption of plant products is necessary to maintain high concentrations of these metabolites in the blood. The pharmacokinetic parameters of resveratrol are half-life of 9.2 h, absorption of 75%, and low oral bioavailability, less than 1%; sulfation and glucuronidation in the small intestine appear to be the limiting steps in bioavailability. Its most important metabolites are glucuronide and resveratrol sulfate (Vélez-Marín et al. 2012). It is extensively metabolized in the liver mostly by glucuronidation and sulfation, the latter carried out by phenol sulfotransferases.

There are multiple positive effects of resveratrol already demonstrated on in vitro models and clinical trials in humans: antiatherosclerotic and cardioprotective effect, antiplatelet, anticancer, antiviral, lipid-lowering, antioxidant, and neuroprotective effect. Resveratrol is available for sale to the public as a dietary supplement, with the premise of losing weight, as a cardiovascular protector and antioxidant, and even to prolong longevity. Most of the current evidence is in animals, and human clinical studies are needed to demonstrate its safety and tolerability (Gambini et al. 2013).

Flavonoids, including resveratrol, are associated with numerous mechanisms of action, which exert beneficial effects in various conditions including obesity, metabolic syndrome, type 2 diabetes mellitus, cancer, dementia, and Alzheimer's. Resveratrol metabolites are found primarily in the liver, compared to muscle and

Table 9.1 Immunomodulation effects of resveratrol in various pathologies

Bioactivity	Effect	References
Antioxidant activity	The antioxidant capacity of resveratrol is due to the inhibition of nicotinamide adenine dinucleotide phosphate oxidases, reducing ROS and increasing the levels of mRNA of antioxidant enzymes such as superoxide dismutase and catalase	Inglés et al. (2014), Banez et al. (2020)
Anticancer effect	Resveratrol inhibits the expression of FAK, which stops carcinogenesis, and decreases the expression of H-RAS, which controls the cell cycle of tumors. It increases the expression of Bcl-2 and the activation of caspase-3 within cells and increases the expression of Fas, which controls cell death outside them. It also can suppress the protumor activation of tumor-associated macrophages (TAMS) which is associated with malignant and metastatic cancers	Choi et al. (2013), Yoon et al. (2015), Nitulescu et al. (2018)
Anti-inflammatory activity	RSV blocks TyrRS and COX-1, which are chemoattractant molecules, activates SIRT1 which decreases the production of pro-inflammatory molecules such as IL-8 or TNF-α, and also reduces the expression of ICAM-1, decreasing the adhesion of white cells	Latruffe et al. (2015), Berman et al. (2017)
Antihypertensive activity	Resveratrol causes vasodilation of blood vessels by activating AMP/PK, reducing blood pressure by preventing smooth muscle contraction; it also reduces ICAM-1 expression, preventing HA	Cao et al. (2014), Berman et al. (2017)
Antiviral effect	MERS-CoV, RSV can block the NF-kB pathway preventing the production of inflammation molecules. In HSV, it increases ROS, essential to stop viral infection. It induces the death of B cells infected with EBV by inhibiting the expression of LPM1, an essential protein for infection by this virus; in an infection with IAV, it increases the expression of MHC-1 to stimulate the immune cells that will kill the infected cells	Chen et al. (2012), Teijaro (2016), Taniguchi and Karin. (2018), Saha and Robertson. (2019)
Resveratrol effect in metabolic diseases	RSV plays an important role in obesity by activating SIRT1, which controls the metabolism of lipids and	Howitz et al. (2003), Petrovski et al. (2011), Huang et al. (2020)

(continued)

Table 9.1 (continued)

Bioactivity	Effect	References
	carbohydrates, replacing the lack of physical activity, and increases the absorption of glucose into the cells due to the lack of insulin in DM and the production of NO in the endothelial cells of the blood vessels, acting as a vasodilator and preventing platelet aggregation	
Resveratrol effect in autoimmune diseases	Resveratrol acts on DMT1, binding to insulin to improve glucose absorption; in Crohn's disease, it decreases the expression of MDSCs, which inhibits the activation of effector lymphocytes in the intestine. Reduces the production of IL-17 and IL-19 and activates the apoptosis of keratinocytes which cause psoriasis	Lee et al. (2016), Oliveira et al. (2017)
Resveratrol effect in degenerative diseases	In AD, resveratrol reduces MMP9 expression, decreasing the entry of leukocytes to the brain, and restores memory by eliminating the formaldehyde accumulated by age. In AMD, COPD and DMD have an anti-inflammatory role by reducing the expression of IL-6 and IL-8, preventing the accumulation of leucocytes in damaged sites. Furthermore, it is capable of decreasing serum concentrations of VEGF and CPR, preventing the development of atherosclerotic plaques	Gordon et al. (2013), Lançon et al. (2016), Moussa et al. (2017), Wang et al. (2017a, b), Figueira and González (2018), Liu et al. (2019)

adipose tissue. Resveratrol can be consumed in pills or food, especially fresh foods (Nicol et al. 2020). However, the consumption of functional foods, including fruits and vegetables, is lower than the recommendations (at least five servings a day) in adults.

9.4 Immunomodulatory Role of Resveratrol in Various Pathologies

9.4.1 Antioxidant Activity

Antioxidant compounds are substances that can reduce, modulate, or prevent the oxidation of essential molecules in biological systems, neutralizing pro-oxidant

molecules. Antioxidants prevent the reactive species as free radicals and reactive oxygen and nitrogen species from acting on DNA, lipids, and proteins through neutralizing its oxidative capacity by being oxidized themselves (Ajith et al. 2017; Olszowy 2019). The role of antioxidant compounds can be done by different forms such as scavenging the free radicals; preventing the reactive species formation; forming chelate complexes with pro-oxidant metals, singlet oxygen, and photosensitizers quenching; and removing and repairing damages caused by the reactive species and enzyme deactivation or activation (Oroian and Escriche 2015; Olszowy 2019; Banez et al. 2020; Song et al. 2021).

Resveratrol is a recognized antioxidant compound, with many health benefits associated with low oxidative stress. Resveratrol allows the inhibition of the formation of oxygen free radicals inhibiting nicotinamide adenine dinucleotide phosphate oxidases and subsequent production of reactive oxygen species and induces expression of antioxidant enzymes and their substrates (Banez et al. 2020).

Antioxidants have been widely studied for the treatment of various diseases since the last decades, mainly in the treatment and prevention of cardiovascular and neurodegenerative diseases. Many studies have shown that some antioxidant compounds may also have potential immunoregulatory activity. The effect of immunomodulation resulting by antioxidant effects is less explored; however, the mechanism and effects of all health benefits and immunomodulations of resveratrol have predominantly been attributed to its antioxidant activity and to some extent direct target interaction (Ajith et al. 2017; Prysyazhna et al. 2019).

Some antioxidant molecular mechanisms of resveratrol have been elucidated, as the positive regulation of the phosphatase and tensin homolog, which decreased Akt phosphorylation, leading to an upregulation of antioxidant enzyme mRNA levels such as superoxide dismutase and catalase (Inglés et al. 2014). Resveratrol activates adenosine monophosphate-activated protein kinase to maintain the structural stability of forkhead box O1, facilitating its translocation, and accomplish its transcriptional function (Yun and Lee 2018), and it can reduce the ischemia-reperfusion injury-induced oxidative stress by inhibiting the activation of the p38 mitogen-activated protein kinase pathway; therefore, the levels of antioxidants like glutathione increase, and free radicals are directly reduced (Fu et al. 2018; Meng et al. 2020). Also, resveratrol exhibited antioxidant bioactivities by regulating antioxidant gene expression via the Kelch-like ECH-associated protein 1 pathway and sirtuin 1 (Li et al. 2016).

Currently, resveratrol was associated to attenuate oxidative injury owing to the induced autophagy via the AMPK-mediated inhibition of mammalian target of rapamycin signaling or via the activation of transcription factor EB, which promoted the formation of lysosomes and autophagosomes as well as their fusion into an autolysosome (Zhou et al. 2019).

9.4.2 *Anticancer Effect*

In recent years, the use of resveratrol and other polyphenols for cancer treatment has been widely investigated. The research that was held by Jang et al. (1997) was one of the first reports that mentioned the anticancer activity of resveratrol. They reported that resveratrol could act as a chemopreventive agent by inhibiting tumor formation on murine models of skin cancer. Even though the mechanism was not understandable at all, this study was the pioneer to be able to acknowledge different mechanisms of action that resveratrol exerts on distinct types of cancer.

The anticancer activity of resveratrol is mainly due to it can intervene in different cellular pathways related to apoptosis (Lin et al. 2011). Nevertheless, there are other processes than resveratrol carries out to act against cancer cells, for example, by reducing ROS production and the damage induced by oxidative stress or the contrary, by promoting the production of ROS in cancer cells (Heo et al. 2018; Yan et al. 2018) by increasing immunity in cosurveillance, cell cycle arrest (Ko et al. 2017), stopping the transformation of procarcinogen to carcinogen, among others.

Takashina et al. (2017) reported that resveratrol could induce apoptosis in leukemia cells U937 (Human leukemic monocyte lymphoma) and MOLT-4 (Human acute T lymphoblastic leukemia) by reducing the expression of H-Ras and consequently diminish the activation of Akt. H-Ras activates the PI3/Akt pathway, which controls processes such as apoptosis, cell cycle progression, cell size, and transcription; studies have proven that this pathway is hyperactivated in different types of cancer, resulting in cell survival and apoptosis inhibition. In the same way as the PI3K/Akt pathway, overactivation of Ras is also found in many cancers (Asati et al. 2016; Nitulescu et al. 2018). Other authors have also mentioned the anticancer activity of resveratrol in leukemia. For example, Fan et al. (2018) described that resveratrol could induce cell death in HL-60 cells through autophagy and apoptosis. Resveratrol could activate the intrinsic and extrinsic apoptotic pathways. The first one was triggered by increasing the production of Bcl-2 and following the activation of caspase-3. Contrarily, the extrinsic pathway was stimulated by increasing the expression of Fas and FasL; then caspase-8 was cleavaged to activate other caspases and perform cell death. Also, resveratrol could induce autophagy by inhibiting the negative regulator of autophagy mTOR through the blockage activation of the PI3/Akt pathway. mTOR and PI3K/Akt may activate some oncogenes resulting in the suppression of autophagy and improvement of cancer formation (Choi et al. 2013).

Autophagy plays an essential role in cancer, is related to tumor promotion and suppression, and contributes to cancer cell development and proliferation. Miki et al. (2012) also reported that resveratrol could induce autophagy and apoptosis in colon cancer cells HT-29 and COLO 201. In that study, the activity of Caspase-8/Caspase-3 was increased leading to apoptosis through the death-receptor pathway. Autophagy was also induced by resveratrol and acted as a cell death mechanism; protein LC3-II which is part of autophagosomal membranes was also found in the analysis. Both apoptosis and autophagy were triggered by ROS production; even

though resveratrol is a natural antioxidant, there is evidence that supports that resveratrol and other polyphenols can induce the production of ROS to lead apoptosis in some types of cancer (Juan et al. 2008).

Resveratrol has affected other types of cancer. Buhrmann et al. (2017) investigated the effect of this stilbene in colorectal cancer cells (CRC) HCT116 and SW480. They found that resveratrol reduced CRC invasion and proliferation by enhancing the expression of Sirt1, inhibiting of NF-κB-mediated inflammatory pathway, and suppressing focal adhesion kinase (FAK) activity. That results in a loss of focal adhesion molecules, a planar surface of the CRC cells, and an increase in apoptosis. FAK is a protein that regulates cell adhesion, migration, metastasis, motility, proliferation, and survival (Yoon et al. 2015). In many types of cancers, FAK is overexpressed, including CRC (Kong et al. 2015). The inhibition of FAK results in the suppression of the early stages of carcinogenesis. In addition to this, Buhrmann et al. (2017) reported that resveratrol showed to suppress the activation of NF-κβ, suppressing the transcription of products involved in invasion (MMPs), metastasis (CXCR4) and activating those involved in apoptosis such as cleavage of caspase-3. The blockage of NF-κβ in this study was related to the upregulation of Sirt1. Sirt1 plays a fundamental role in cell death, survival, and immune tolerance. One of the principal substrates of Sirt1 is the p65/RelA, an NF-κB subunit which is the primary regulator of leukocyte activation and inflammatory cytokines signaling. The activation of Sirt1 by resveratrol generates the deacetylation of Re1A. That action attenuates NF-κB-mediated gene transcription of factors that intervene in inflammation pathways, including TNF, IL-1, IL-6, Cox-2, metalloproteases (MMP)-1, and MMP3 (Yamamoto and Gaynor 2001; Lee et al. 2009a, b).

Chai et al. (2017) also mentioned the enhanced expression of Sirt1 by using resveratrol on human hepatocellular carcinoma (HCC) cell lines. They reported that the activation of Sirt1 is related to the deacetylation of FoxO1, which leads to tumor suppression in HCC cells. Also, Sirt1 acts as a negative regulator of the PI3K/Akt pathway, which is involved in cell proliferation, tumor growth, and metastasis (Jiang et al. 2020). Resveratrol also showed to diminish the production of antiapoptotic proteins Bcl-2/Bax and enhanced the activation of caspase-3 and caspase-7. In another study, resveratrol also had activity against liver cancer. Bishayee et al. (2010) demonstrated that resveratrol combats oxidative-nitrosative stress and suppresses the inflammatory cascade during liver carcinogenesis through the overexpression of Nrf2. Nrf2 is a protein that protects cells against oxidative-nitrosative stress. The generation of ROS and reactive species of nitrogen (RON) is a crucial factor in the initiation and progression of hepatocarcinoma. Oxidative-nitrosative stress also is involved in invasion, migration, and metastasis of HCC (Fu and Chung 2018).

Furthermore, Sun et al. (2017) suggested that resveratrol could effectively inhibit lung cancer progression by suppressing the protumor activation of tumor-associated macrophages (TAMs). TAMs play a crucial role in cancer progression, evasion of immunity, and dissemination of cancer cells. They are associated with tumor malignancy and relapse. Sun et al. (2017) reported that resveratrol inhibited the alternatively activated macrophage (M2) polarization of TAMs through the

inhibition of STAT 3 activation, a transcription factor that is involved in M2 polarization cell cycle progression and promotion of antiapoptosis and proliferation. The inhibition of STATs signaling pathways can suppress tumor growth and metastasis by inhibiting M2-like polarization of macrophages, further suggesting that TAMs are a possible target in cancer therapy. Additional evidence suggests the role of resveratrol in tumor growth, Kimura and Sumiyoshi (2016) reported that resveratrol prevented tumor growth and metastasis in mice models with osteosarcoma. According to this report, resveratrol prevented lung and liver metastasis by different mechanisms of action. One of them was by stopping the activation and differentiation of M2 in TAMs through the suppression of STAT3. The other was by diminishing the expression of lymphatic vessel endothelial hyaluronan receptor-1 (LYVE-1). This protein is widely expressed in the endothelium of lymphatic vessels of tumors and promotes lymphangiogenesis, metastasis, and tumor growth (Hara et al. 2018).

Even though the potential of resveratrol as a chemopreventive and chemotherapeutic agent is promising, there are still crucial points that must be studied thoroughly. Among these points are resveratrol's bioavailability, route administration, formulation, and possible interaction with other compounds (Ko et al. 2017).

9.4.3 Anti-inflammatory Activity

Inflammation is an immune response to an injury or the presence of an antigen in the body; it is characterized by pain, redness, heat, swelling, and even the loss of tissue function (De Sá-Coutinho et al. 2018); it is normally linked to a large number of diseases (Latruffe et al. 2015). Inflammation is the result of the signaling of chemokines and interleukins that move leukocytes to the damaged site; this is possible due to the release of pro-inflammatory molecules such as prostaglandins and leukotrienes (Latruffe et al. 2014). Resveratrol is a molecule capable of modulating different enzymes that intervene in this immune response like kinases, lipoxygenases, cyclooxygenases, and sirtuins, in addition to eliminating free radicals present in cells (De Sá-Coutinho et al. 2018).

Resveratrol can suppress inflammation by different mechanisms, which stand out: aminoacyl-tRNA synthetases enzymes play an important role in inflammation; tyrosine-tRNA-ligase (TyrRS) is normally inactive, but through natural proteolysis, it fragments and forms mini-TyrRS which is a chemoattractant of leukocytes acting like IL-8; and resveratrol has the ability to bind to the catalytic site of mini-TyrRS and inhibit it causing an anti-inflammatory effect (Latruffe et al. 2015). Enzymes such as prostaglandin-H synthetase, cyclooxygenase (COX), and lipoxygenase are involved in the main route of synthesis of pro-inflammatory mediators from the arachidonic acid (AA). Resveratrol can bind to the COX-1 catalytic site preventing AA from catalysis. In addition, it decreases the expression of COX-2 through two transcription factors: NF-κB and the AP-1 complex, which are controlled by an IKKB/MAPK signaling cascade. Resveratrol prevents the phosphorylation of these

kinases causing the decrease in the secretion of pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α and increasing the anti-inflammatory cytokines, also reducing the expression of adhesion proteins (ICAM-1) that help to the mobilization of leukocytes (Latruffe et al. 2015). Resveratrol also activates the silent information regulator T1 (SIRT1), affecting the nuclear factor kB (NF-kB) signaling pathway, which deacetylates the RelA/p65 subunit of nuclear factor kB. NF-kB is present in the cytoplasm of macrophages linked to an inhibitory protein Ikβ; when it is phosphorylated, NF-kB is released and goes to the nucleus to activate the transcription of genes involved in the inflammatory response, such as tumor necrosis factor-α (TNF-α), interleukin 1β (IL-1β), nitric oxide synthase (iNOS), and increasing vascular permeability (Berman et al. 2017). Resveratrol is capable of attenuating the activity of the microsomal enzyme-prostaglandinE-synthetase-1 (mPGES-1) which is responsible for the synthesis of PGE. (Moller et al. 2015). Another mechanism involves the toll-like receptor 4; it is an important initiator in the inflammatory response that, once activated, myeloid differentiation factor 88 (MyD88) binds to it and activates NF-kB and therefore begins the production of cytokines pro-inflammatory; resveratrol significantly reduces the levels of TLR4 and MyD88, having an anti-inflammatory effect (Zhang et al. 2016). Resveratrol is a powerful activator of poly (ADP-Ribose) polymerase 1 (PARP1), which is capable of inhibiting the action of COX-2 and increases the production of B-cell lymphoma-6 protein (BCL6) which has the ability to recruit monocytes in an inflammatory environment (Yanez et al. 2019).

Latruffe et al. (2015) observed the action of resveratrol in THP-1 monocyte cells; this increased the expression of miRNA-663, which is directed to suppress genes involved in the immune response, such as JUNB and JUND transcription factors, and also decreases the transcription factor AP-1 activity, which is normally activated by inflammatory cytokine stimuli. Wang et al. (2013) experimented with obese mice giving them a resveratrol supplement to study its anti-inflammatory potential; the results showed a decrease in TNF-α and IL-6 and an increase in IL-10 in a dose-dependent manner.

Szkudelsk et al. (2020) studied the anti-inflammatory properties of RSV in diabetic rats, he noted that the content of inflammatory mediators such as IL-6, IL-1β, TNF-α, and NF-κB was low in skeletal muscle; however, in the adipose tissue, release of these mediators was increased. Szkudelsk et al. (2020) reported that the efficacy of resveratrol is tissue-specific. Wang et al. (2017a, b) did studies with acute inflammation in rats, comparing the effectiveness of dexamethasone (DXM) and resveratrol at different concentrations; in a xylene-induced edema, the degree of inflammation was dose dependent, reaching the same effectiveness as the DMX. He also caused an allergic inflammation, where mast cells release inflammatory mediators and attract leukocytes; however, when treating them with resveratrol, the number of leukocytes found in the area was low, which confirms the anti-inflammatory capacity of resveratrol.

Senturk et al. (2018) made a wound in the spine of mice, treated it with resveratrol, and had a notable reduction in the levels of pro-inflammatory cytokines; this was confirmed by the increase in healthy glial cells and motor neurons.

There is an inflammatory response in the pancreas due to insulin resistance as one ages, Calvo et al. (2017) administered resveratrol in elderly mice, which had an overexpression of pro-inflammatory cytokines; after treatment, a lower expression of TNF-α was observed and IL-1β, as well as NF-κB p52; however, there was no increase in anti-inflammatory interleukins such as IL-10.

Zhou et al. (2018) induced acute pharyngitis in rabbits, treatment with RSV inhibited the activity of macrophage inflammatory protein 2 (MIP-2) and COX-2, and it also stopped the increase in caspase-3/9 activity, which acts on the cell death. In addition, low serum levels of TNF-α and IL-6 were observed. Likewise, Zhou et al. (2018) demonstrated that resveratrol decreases the expression of TLR4 and MyD88, which represent a pro-inflammatory signaling pathway.

Asthma is an inflammatory disease characterized by excessive infiltration of leukocytes, mainly eosinophils, in the airways, causing bronchoconstriction. Lee et al. (2009a, b) experimented in mice, administering resveratrol as a treatment, and observed a decrease in the migration of white cells; the amount of immunoglobulin E and the concentration of IL-4 and IL-5 in the lungs were also reduced. IL-5 is known to stimulate eosinophils's degranulation, so resveratrol stops or decreases the inflammatory response.

Owing to its great anti-inflammatory capacity, resveratrol could be used as a drug for different diseases closely linked to inflammation; however, its bioavailability within the body is very low, which limits its application (Malhotra et al. 2015).

9.4.4 Antihypertensive Activity

Hypertension is a disease that affects approximately 25% of adults worldwide, and some hypertensive patients are resistant to blood pressure reduction with actual antihypertensive drugs. Different complications are associated with hypertension, including end organ damage, stroke, left ventricular hypertrophy, and arteriosclerosis. The number of people with metabolic syndrome is growing and contributes to the increase in hypertension cases, which is creating an important alarm for the search for new compounds or treatments to avoid cardiovascular complications (Dolinsky et al. 2013).

A recent study showed the ability of resveratrol to induce vasodilation by oxidative activation of protein kinase 1α and reduced blood pressure in hypertensive wild-type mice. This activity was explained by the oxidation of phenolic rings of resveratrol that paradoxically leads to oxidative modification of proteins, elucidated by formation of a reactive quinone that oxidizes the thiolate side chain of cysteine residues, which were improved in cells under oxidative stress (Prysyazhna et al. 2019).

Resveratrol showed to affect the activity of vascular smooth muscle cells and to inhibit the expression of vascular cell adhesion molecules, which are responsible for hypertension and the development of atherosclerosis, respectively (Berman et al. 2017).

Grujic-Milanovic et al. (2017) demonstrated that resveratrol from red wine improves the hemodynamics oxidative defense and aortal structure in essential and malignant hypertension. Resveratrol exerts vasorelaxant properties, provides protection of endothelial milieu, acts as pleiotropic cellular effector, and developed hypertrophy in female rat aorta. The results suggest that resveratrol may act in vivo by reduction of free radicals, activation of antioxidant enzymes, removing of superoxide anions, and promotion of nitric oxide availability, hydroxyl radicals, and lipid peroxyl radicals. An important finding was the activation of AMP-activated protein kinase induced by resveratrol and reduces blood pressure inhibiting human vascular smooth muscle cells contractility through the suppression of myosin phosphatase-targeting subunit 1 and myosin light chain phosphorylation (Cao et al. 2014).

The treatment of hypertensive rats with resveratrol attenuates development of hypertension and prevents endothelial dysfunction. The mechanisms proposed by resveratrol effect was the attenuation of vascular oxidative stress resulting in increased nitric oxide bioavailability, increased expression of important proteins in nitric oxide pathway, and prevention of endothelial nitric oxide synthase uncoupling possibly via inhibition of cofactor tetrahydrobiopterin oxidation by free radicals (Bhatt et al. 2011). A meta-analysis of six randomized controlled human trials (including 247 subjects) showed that high doses of resveratrol (>150 mg/day) significantly decreased blood pressure, while lower doses had no effect (Liu et al. 2015).

9.4.5 Antiviral Effect

Resveratrol is one of the most well-known stilbenes and, as mentioned in previous lines, is found in several natural sources. According to different studies, this compound has shown multiple biological activities (Malaguarnera 2019); most of them, including antiviral activity, are related to the immunomodulatory role that resveratrol can exhibit. The antiviral activity of resveratrol has widely investigated, in different studies, this effect is associated with cell signaling pathways, its interaction with inflammatory signaling transduction, and the upregulating and downregulating of genes involved in apoptosis (Abba et al. 2015; Malaguarnera 2019). In the following paragraphs, a few examples will be discussed.

Lin et al. (2017) reported that resveratrol was able to inhibit the infection of Middle East respiratory syndrome coronavirus (MERS-CoV) by different mechanisms of action. One of these mechanisms was by blocking the NF-κβ pathway, which involves the downregulating inflammatory signaling. The activation of NF-κβ is necessary to produce inflammatory cytokines. It is worth mentioning that MERS-CoV infection induces the production of pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-8, among others causing several effects or even death in patients (Lau et al. 2013). By blocking the NF-κβ pathway, cells are not able to carry out the transcriptional activity to produce these kinds of molecules (Taniguchi and Karin

2018). Xie et al. (2012) also mentioned the anti-inflammatory effect of resveratrol. It is reported in their study that the stilbene inhibited the production of IL-6 in 9HTEo cell lines infected with the respiratory syncytial virus (RSV) by controlling the expression of Toll-like receptor 3 (TLR-3) and, thus, the suppression of Toll/IL-1R domain-containing adaptor-inducing IFN-β (TRIF). TRIF is an adaptor of TL3 and is involved in the activation of NF-κβ. As mentioned before, NF-κβ is necessary to produce different cytokines; in consequence, the changes in the expression TL-3 and TRIF may decrease the production of IL-6. Also, Xie et al. (2012) reported that resveratrol could suppress the expression of TANK-binding kinase 1 (TBK1). This molecule also participates in NF-κβ activation by inducing Iκβ degradation. Therefore, the suppression of TBK1 also is involved in the inhibition of IL-6 production. Other authors also explain the blockade of NF-κβ by resveratrol. For example, Faith et al. (2006) and Annunziata et al. (2018) reported that resveratrol blocks NF-κβ inhibiting the replication of herpes simplex virus (HSV). However, some reports suggest other antiviral mechanisms against HSV by resveratrol and its derivatives. For example, Chen et al. (2012) reported that a derivate from resveratrol was able to inhibit HSV infection by increasing the production of reactive oxygen species (ROS). Docherty et al. also proposed this mechanism against HSV by using resveratrol in cutaneous lesions. ROS play an essential role during the activation of the innate immune response during viral infection, including autophagy, gene expression, and signal transduction. It is well-known that polyphenols are antioxidants, but they can also act as pro-oxidants in a dose-dependent manner (Soares et al. 2018). That could explain the mechanism of action of resveratrol during the infection of HSV according to different authors. Another member that belongs to *Herpesviridae* family and has been inhibited by resveratrol is Epstein-Barr virus (EBV). According to Espinoza et al. (2012), resveratrol was able to interrupt the immortalization process associated with EBV infection in human B cells by inducing apoptosis in infected cells. This mechanism starts when resveratrol inhibits the expression of the latent membrane protein 1 (LPM1), which is essential for EBV-transformation of B cells since it acts as a homolog of CD40 and activates multiple cellular pathways such as NF-κβ, AKT, JNK, STAT-3, and p38. They are involved in the regulation of cellular apoptosis and proliferation, for example, by elevating the expression of Bcl2, an antiapoptotic protein (Saha and Robertson 2019). Furthermore, Espinoza et al. (2012) described that resveratrol blocks the activation of NF-κβ and suppresses the production of IL-6 and IL-10; both of these interleukins also contribute to the proliferation and survival of infected B cells.

Resveratrol has also counteracted other viral infections. Lin et al. (2015) reported that resveratrol was able to inhibit influenza A virus (IAV) replication by increasing the production of IFN-β in infected cells. They suggest that resveratrol enhances the expression of TLR-9, which is involved in the activation of interferon-alpha and beta (IFN-α/β) genes through IFN regulatory factor 7 (IRF7) phosphorylation (Sun and Reddy 2013). The activation of IRF7 mainly leads to the production of IFN-β. IFN-β can inhibit virus propagation and stimulate the adaptative immune response by promoting the MHC-I expression on various cell populations. MHC-I is essential

for T-cell stimulation, differentiation, and expansion and killing of cells that have infected with the virus (Teijaro 2016). Summarizing this, resveratrol and IFN-β work synergistically to inhibit the replication of influenza A virus in lung cells. Even though IFN-α/β response is one of the first lines of defense against viral infections, it is reported that in some cases of infection by influenza viruses, this response is diminished due to these viruses employ mechanisms to evade and antagonize the effect through the nonstructural protein 1 (NS1) (Killip et al. 2015), PB1-F2 protein (Dudek et al. 2011), and viral polymerase (Iwai et al. 2010). Resveratrol has tested against other respiratory viruses. Mastromarino et al. (2015) studied the effect of this polyphenol facing a strain of human rhinovirus (HRV). They reported reduced levels of inflammatory cytokines such as IL-6, IL-8, and RANTES by using resveratrol. This reduction of interleukins is related to the blockage of NF-κβ. Also, it is worth to mention that RANTES and IL-8 are produced in high quantities during HRV infection comparing to other viruses such as adenovirus and resveratrol (Chun et al. 2013). The elevated production of these cytokines produces severe inflammation in the host. In particular, IL-8 acts as a mediator to activate neutrophils, and they contribute to airway obstruction following severe asthma (Krawiec et al. 2001; Wark et al. 2002). According to Mastromarino et al. (2015), resveratrol was also able to inhibit HRV replication by diminishing the expression of intercellular adhesion molecule 1 (ICAM-1), also known as CD54. During HRV infection, ICAM-1 is overexpressed and is used by HRV to enter into the respiratory epithelium and start the replication (Xing et al. 2003; Shukla et al. 2017).

The several studies that prove the immunomodulatory-antiviral role of resveratrol could lead to the development of alternative therapies for the treatment of viral diseases.

9.4.6 Resveratrol Effect in Metabolic Diseases

Obesity is a global health problem. The World Health Organization (WHO) indicates that obesity has almost tripled since 1975. In 2016, more than 1.9 billion adults over 18 years of age were reported overweight of these. The world health organization estimates that 650 million are obese. Obesity is an abnormal or excessive accumulation of fat that is detrimental to health (WHO 2020a).

Obesity damages people's health because it is a significant risk factor for developing cardiovascular diseases, insulin resistance, and type 2 diabetes mellitus (Fruh 2017). Obesity is characterized by the accumulation of fat in adipose tissue. However, there is a risk that fat accumulates in non-adipose tissues such as the liver and skeletal muscle. Causing other diseases such as the fatty liver and decreased sensitivity to insulin, it is related to reduced insulin sensitivity (de Ligt et al. 2015).

Resveratrol is a polyphenolic phytoalexin widely studied for multiple properties. One of these approaches is the use of resveratrol for the treatment of metabolic diseases. Therefore, the mechanisms of action of resveratrol in cells as a regulator of

metabolism have been elucidated; however, it is not yet fully understood, and more human clinical studies are lacking (Szkudelska and Szkudelski 2010).

Resveratrol is an activator of the deacetylase sirtuin 1 (SIRT1) protein gene that is believed to regulate lipid and carbohydrate metabolism; its primary function is to maintain normal cell energy levels (Howitz et al. 2003). Resveratrol can activate the expression of SIRT1 directly or indirectly through the activation of AMP-activated protein kinase (AMPK) (Howitz et al. 2003; Baur et al. 2006). In addition to resveratrol, SIRT1 activation can be induced by exercise and calorie restriction in the diet. The resveratrol resembles the mechanism that physical activity and hypocaloric diet can perform in cellular metabolism (Ruderman et al. 2010).

The mitochondria of muscle cells show a reduction in the oxidative capacity of fat in obesity. Peroxisome proliferator-activated receptor γ co-activator 1 α (PGC-1 α) is a regulatory protein of mitochondrial biogenesis and metabolism. In addition, it binds to specific transcription factors that participate in the expression of mitochondrial proteins that increase their activity. The participation of PGC-1 α as an effector protein in the activation of the AMPK-SIRT1 signaling cascade of lipid and carbohydrate metabolism has been reported (Mihaylova and Shaw 2011).

A reduction in the expression of the PGC-1 α gene has been found in people with type 2 diabetes mellitus, suggesting that the decrease in the expression of PGC-1 α leads to a reduction in mitochondrial function and, consequently, a decrease in sensitivity to insulin in the muscle (Mootha et al. 2003). The physical activity and reduction of the calorie intake improve the function of the oxidative capacity of the mitochondria of the muscle cells and increase the sensitivity to insulin. Calorie restriction for 6 months increases the expression of AMPK, PGC-1 α, and SIRT1 and also reduces insulin levels (Civitarese et al. 2007).

Animal studies have been conducted to understand the effect of resveratrol on the oxidative activity of the mitochondria of muscle cells. Resveratrol influences mitochondrial biogenesis by activating the AMPK-SIRT1-PGC-1 α signaling pathway. Resveratrol induces a reduction in adipogenesis and decreases the size of adipocytes. This was tested in mice on a high-calorie diet (Lagouge et al. 2006). Resveratrol, combined with a hypercaloric diet, increases the survival and motor function of mice, in addition to changing gene expression towards normal expression in mice with a normal diet (Baur et al. 2006; Lagouge et al. 2006). Resveratrol has also been found to inhibit adipogenesis (Rayalam et al. 2008).

Diabetes mellitus is a chronic disease that occurs because the pancreas does not produce insulin or defects in the use of insulin. It is classified as type 1 and 2. Type 1 diabetes is caused by the destruction of the beta cells of the pancreas by autoantibodies, there is no insulin production. Type 2 diabetes is due to abnormal secretion and action of insulin. Both types cause hyperglycemia, which, over time and poor control, can damage organs (WHO 2020b).

Resveratrol regulates the metabolism of carbohydrates in different ways according to what has been documented, mainly by reducing the concentration of glucose in the blood; it has also been reported to improve the action of insulin and protect the beta cells of the pancreas (Szkudelski and Szkudelska 2011).

Animal models with diabetes have been used to assess the effect of resveratrol. Finding a decrease in the levels of glycated hemoglobin (HbA1c) reflects the reduction in blood glucose levels (Palsamy and Subramanian 2010). The reduction in blood glucose is because resveratrol increases glucose uptake by cells in the absence of insulin (Huang et al. 2020). Also, there are reports that it stimulates the expression of insulin-dependent glucose transporter (GLUT4), which was tested in a study in rats with induced diabetes and treated with resveratrol compared to the control group of rats with induced diabetes without resveratrol (Penumathsa et al. 2008). Insulin resistance occurs when cells do not respond to insulin. It mainly affects people who are overweight or obese. Exercise and a low-calorie diet decrease adipose tissue thus improving insulin sensitivity. A study in mice fed a high-fat diet in conjunction with resveratrol improved insulin sensitivity compared to the group that only received the high-fat diet without resveratrol (Baur et al. 2006).

On the other hand, a clinical study carried out in male patients with obesity found the administration of resveratrol, 75 mg twice a day for 30 days, had effects on carbohydrate metabolism, reducing the blood glucose and improving insulin sensitivity. In muscle cells, improvement in mitochondrial function by activating the AMPK-SIRT1- PGC-1a pathway decreased levels of triglycerides, inflammation markers, and intrahepatic lipids (Timmers et al. 2011).

Cardiovascular disease is a health problem. This group of diseases includes high blood pressure, coronary artery disease, and atherosclerosis. Genetic factors and environmental factors such as poor diet and sedentary lifestyle influence the development of these pathologies. In atherosclerosis, the use of resveratrol at physiological concentrations in the consumption of wine increases the expression of the enzyme NO synthase that participates in the production of nitric oxide (NO) that functions as a vasodilator in the endothelial cells that form the blood vessels and decreases the expression of endothelin (ET) that functions as a vasoconstrictor. Resveratrol works as a cardioprotective agent by inhibiting platelet aggregation. In atherosclerosis, resveratrol decreases the production of cytokines IL-6 and IL-8 and granulocyte-macrophage colony-stimulating factor (GM-CSF). Also, resveratrol prevents the oxidation of low-density lipoprotein (LDL) from preventing its adherence to the blood vessel. Hypertension is characterized by increased heart weight, elevated blood endothelin (ET) and angiotensin II, and decreased NO (nitric oxide). Resveratrol reduces heart weight, ET, and angiotensin II expression, while increasing NO concentration (Petrovski et al. 2011).

9.4.7 Resveratrol Effect in Autoimmune Diseases

The immune system is responsible for maintaining homeostasis in the body by protecting it from pathogenic microorganisms and developing abnormal cells through different mechanisms that lead to the activation of specialized cells. However, when these mechanisms are abnormal, the immune system attacks cells, organs, and tissues. Currently, more than 80 autoimmune diseases are known.

Autoimmune diseases happen by losing tolerance towards self-antigens, pro-inflammatory cells, and auto-antibodies (Ramos et al. 2015). Resveratrol as a possible therapeutic alternative for autoimmune diseases has had favorable results according to various studies.

Type I diabetes mellitus is a disease in which autoantibodies are produced that destroy the pancreas beta cells, which are cells specialized in the production of insulin, which is an essential hormone for the transport of glucose to the cells and its deficiency causes hyperglycemia. Hyperglycemia is related to a decrease in antioxidant agents and an increase in oxidative stress due to the activation of the NF-kappaB pathway, promoting pro-inflammatory cytokines and adhesion molecules (Chang et al. 2012).

The immunological process that takes place in this disease is pro-inflammatory activity. The activation of pro-inflammatory cytokines promotes apoptosis of beta cells of the pancreas islets in an environment of oxidative and inflammatory stress (Palsamy and Subramanian 2010). Resveratrol has antioxidant properties and can act by scavenging free radicals. It also has anti-inflammatory properties, since it suppresses the activation of the NF-kappaB pathway and expression of cytokines (Zhang Hanrui et al. 2009; Lee et al. 2011).

Resveratrol acts in different ways in DM1: it inhibits Th1 cells by binding to the chemokine receptor 6 (CCR6 receptor). Resveratrol binds to insulin to promote glucose uptake. Resveratrol activates the deacetylase sirtuin 1 (SIRT1) pathway, increasing oxidation during cellular stress to decrease the concentrations of reactive oxygen species (ROS) and prevent damage to the pancreas beta cells (de Oliveira et al. 2017).

Crohn's disease and ulcerative colitis are chronic and inflammatory diseases that affect the intestine, originate from a combination of genetic, environmental, immunological, and microbiological factors. These diseases are caused by changes in the intestinal mucosa, causing the release of bacteria that induce the immune system activation. Crohn's disease is the result of the combination of genetic factors that increase the susceptibility to the disease, environmental factors, and the intestinal microbiota, resulting in an abnormal immune response in the intestinal mucosa that affects the cells that line the intestine due to the inflammation produced by the immune response (Torres et al. 2017).

Activation of the NF-kappaB pathway occurs to produce cytokines in response to bacterial fragments recognized by NOD-like receptors, which causes the activation of Th1 and Th17 cells. In ulcerative colitis, the inflammation affects the colon, rectum, and distal colon. There is the activation of Th2 and Th17 lymphocytes, releasing pro-inflammatory mediators such as ROS and TNF-a (de Oliveira et al. 2017; Shi et al. 2017). Oxidative stress occurs in both diseases with the release of ROS, NO (nitric oxide), MDA (Malondialdehyde), and MPO (myeloperoxidase) and inhibition of antioxidant enzymes such as sod and GP (glutathione peroxidase). It was producing an inflammatory response. Resveratrol works by inhibiting inflammatory cytokines and neutralizing ROS. Preventive treatment with resveratrol works by reducing tissue damage and oxidative stress and was determined by measuring

the reduction in malondialdehyde and the increase in glutathione peroxidase (Nunes et al. 2018).

There is also a decrease in pro-inflammatory cytokines. The microbiota increase improves the intestinal health bifidobacteria and lactobacilli (Larrosa et al. 2010). Studies in humans have found that an administration of 500 mg/day of resveratrol for 6 weeks interrupts the activation of NF-kappaB in mononuclear cells of peripheral blood. In plasma, there is a decrease in TNF-a and C-reactive protein (Samsamikor et al. 2016). Block the activation of TH1 lymphocytes by inhibiting the secretion of IL-1, IL-6, and TNF-a. Also, resveratrol induces immunosuppression of myeloid-derived suppressor cells (MDSCs) in the colon, suppressing the activity of effector lymphocytes (Singh et al. 2012).

Psoriasis is a skin disease associated with dysregulations in the interaction of the immune and adaptive system with skin cells. The mechanism of this disease is controlled by the immune system, mainly dendritic cells and T lymphocytes. Cathelicidin peptide LL-37 initiates it, and the host DNA forms complexes recognized by dendritic cells, which produce interferon-a and other inflammatory mediators such as TNF-a and interleukin-23. TNF-a induces secondary mediators and binding molecules that participate in psoriasis, activating the keratinocytes that release antimicrobial peptides, cytokines, and chemokines that act as attractants of immune cells. The most reported symptoms are pain, itching, and bleeding (Boehncke 2015).

Resveratrol has long been used for its anti-inflammatory properties. In vitro studies have shown that resveratrol induces cell death of the keratinocyte cell line HaCaT through the activation of SIRT1 that inhibits protein kinase B (Akt). This protein participates in the regulation of cell proliferation (Lee et al. 2016). In vivo studies in mice with induced psoriasis were treated with resveratrol, concluding that resveratrol reduce symptoms such as itching and decreases the production of cytokines that participate in the development of psoriasis such as IL-17 and IL-19 (Kjær et al. 2015).

Rheumatoid arthritis is a disease in which the immune system is involved. Immune complexes are created to mediate complement activation and cellular response against self-antigens. In its development, genetic factors that play an important role in the disease risk, severity, and progression are involved in this development, such as the genetic susceptibility of the HLA (human leukocyte antigen), HLA-DRB1, the gene encoding the non-receptor protein tyrosine phosphatase type 22 (PTPN22) and cytotoxic T-lymphocyte associated protein 4 (CTLA)-4) (de Oliveira et al. 2017). In addition to environmental factors such as stress, smoking and obesity (Firestein and McInnes 2017).

The disease is characterized by chronic inflammation of the joints that can destroy cartilage and bone erosion. In the immunological response, there is a loss of tolerance towards self-antigens. Therefore, there is an activation of T lymphocytes by macrophages. Adhesion molecules (CAMs) participate. Cytokines such as IFN-g, IL-12, IL-21, and IL-23. IL-6 are related to synovial inflammation, cartilage, and bone destruction. TNF-a acts on chondrocytes, which release matrix

metalloproteinase (MMP) that degrades cartilage and bone destruction (de Oliveira et al. 2017).

Resveratrol has anti-inflammatory activity by modulating cytokine secretion, TNF-a, and IL-1b (Ma et al. 2015). In vitro studies with fibroblast-like synoviocytes (FLS) treated with resveratrol decrease the generation of ROS and COX/PGE2. It was concluding that resveratrol modulates the inflammatory response (Tsai et al. 2017). In vivo studies concluded that resveratrol administration intra-articularly in an animal model significantly reduces cartilage destruction and reduces inflammation (Elmali et al. 2007).

9.4.8 Resveratrol Effect in Degenerative Diseases

Resveratrol can cross the blood-brain barrier (BBB), which means it has a neuroprotective effect against neurodegenerative diseases (Zhang et al. 2018). The mechanisms of inflammation in the brain are closely linked to age; the main characteristic is the presence of reactive glial cells, which release pro-inflammatory mediators such as prostaglandins, cytokines, and reactive oxygen species; however, it is the response to maintain homeostasis of the brain (Liu et al. 2019).

Alzheimer's (AD) is a disease that causes dementia and decreases the cognitive capacity of patients (Ahmed et al. 2016); it is developed by the presence of dense β-amyloid plaques (Aβ) and neurofibrillary tangles in the CNS (Bastianetto et al. 2015). This disease causes the degeneration of neurons and, therefore, of the neuronal connections, causing an inflammatory environment throughout the brain area, and the activation of glial cells (phagocytic brain cells). The resveratrol had a protective effect by reducing the matrix metalloproteinase 9 (MMP9) of the cerebrospinal fluid, which decrease the permeability of the BBB and therefore limits the entry of leukocytes and inflammatory mediators to the brain (Moussa et al. 2017). Resveratrol will mitigate the action of NF-kB, inhibiting the secretion of PGE, TNF-α, and IL-6 and the expression of MCP-1 mRNA (Lu et al. 2010). Due to the accumulation of Aβ, the expression of nitric oxide synthetase (iNOS) is increased, which leads to cell apoptosis; this pro-inflammatory molecule is decreased with resveratrol in a dose-dependent manner. Resveratrol improves long-term memory by increasing brain-derived neurotrophic factor (BDNF); in addition, with advancing age, formaldehyde accumulates in the brain which is eliminated by resveratrol; this can restore memory (Liu et al. 2019). In addition to this, resveratrol binds to β-amyloid peptides, inhibiting their aggregation, and binds to β-amyloid plaques to break them, which reduces the progress of AD (Ahmed et al. 2016).

Parkinson's disease (PD) is a neurodegenerative disease characterized by the presence of Lewis bodies, formed by α-synuclein, causing the loss of dopaminergic neurons (Feng et al. 2018). The accumulation of Lewis bodies will cause an inflammation response, activating microglial cells which increase the production of pro-inflammatory mediators such as TNF-α and IL-1β, as well as the activation of

astrocytes that release large amounts of species reactive oxygen which causes the death of neurons. Different effects of resveratrol are known, one of them is the decrease in miRNA-214 which is involved in the synthesis of α-synuclein (Wang et al. 2015) and another is reducing the levels of activated astrocytes and microglial, in a dose-dependent manner (Zhang et al. 2018). Liu (2019) indicates that resveratrol reduces the levels of IL-1β and TNF-α and inhibits cellular apoptosis by increasing the expression of Bcl-2 and decreasing the expression of Bax, an antiapoptotic molecule.

Age-related macular degeneration (AMD) is one of the main causes of vision loss in adults; the retinal pigment epithelium (RPE) is responsible for phagocytizing or degrading the photoreceptor segments in the eyes, which creates an environment of oxidative stress in addition to inflammation. Lançon (2016) reported that the treatment of AMD with resveratrol has an anti-inflammatory effect; it decreases the expression of IL-6, IL-8 and inhibits the production of cell adhesion molecules (ICAM-1) and protein monocyte chemoattractant (MCP-1), which reduces the accumulation of leukocytes, mainly neutrophils, in the affected area.

Chronic obstructive pulmonary disease (COPD) is a disease characterized by persistent respiratory symptoms and a very noticeable shortness of breath, which can be caused by a respiratory disease, alveolar abnormalities, or the parenchymal destruction of the lungs. Therefore, a severe inflammatory environment is generated in all the patient's airways, which aggravates the disease. Treatments carried out with resveratrol showed an increase in the expression of SIRT1 and PCG-1 mRNA, which are transcription factors that regulate the secretion of inflammatory mediators such as IL-6 or IL-8, which are markedly decreased; in addition, the resveratrol causes a decrease in the infiltration of white cells, freeing space in the pulmonary alveoli, thus improving air flow (Wang et al. 2017a, b).

Atherosclerosis is a thickening of the intimal layer of blood vessels caused by the recruitment of lymphocytes and monocytes when there is some injury to the vessel wall, generating a large amount of cytokines (Chen et al. 2018). This will decrease the lumen of the vessel and, therefore, the supplementation of oxygen, which causes the release of vascular endothelial growth factor (VEGF); therefore, inflammation and angiogenesis play an important role in this disease. Also, the C-reactive protein, which increased in atherosclerosis, promotes the expression of cell adhesion molecules (ICAM), stimulating the migration of leukocytes to the site and inducing the secretion of pro-inflammatory factors such as IL-6, IL-8, and NF-kB. Studies show that treatment with resveratrol was able to reduce serum concentrations of VEGF and CRP, decreasing endothelial permeability and stopping the formation of atherosclerotic plaques (Figueira and González 2018). In addition, Seo (2019) indicates a decrease in the expression of adhesion molecules in the vascular endothelium, which reduces the accumulation of leukocytes.

Osteoporosis is an age-related disease, caused by the resorption of bone tissue, usually by an imbalance in the activity of osteoblasts and osteoclasts present in the bones. Osteoblasts are the cells responsible for the formation of bones; therefore, their inactivation is the main cause. It has been reported that the overexpression or deletion of silent information regulator transcription 1 (SIRT1) increases or

decreases bone mass; resveratrol is an activator of SIRT1, so it helps to have a balance between osteoblasts and osteoclasts, which has repercussions in the formation of bones. In addition, it has been registered that resveratrol helps maintain mineral density in bones (Yang et al. 2019). On the other hand, active osteoclasts are responsible for bone resorption, eliminating bone tissue and releasing minerals into the blood; the resveratrol will intervene in the activation of osteoclasts, stimulating the release of the inhibitory factor of osteoclastogenesis (OPG). The Fox01 protein functions for the inhibition of osteoclastogenesis and is required for the proliferation of osteoblasts; resveratrol improves Fox01 transcription by inhibiting the PI3K/AKT signaling cascade which keeps Fox01 phosphorylated, preventing its expression (Feng et al. 2018).

Duchenne muscular dystrophy (DMD) is a genetic disease linked to the X chromosome, which results in the translation of the dysfunctional protein dystrophin; this has an important role to join the intracellular cytoskeleton with the extracellular matrix of the muscles. Without this connection, the muscles are easily damaged causing a persistent state of inflammation. There will be regeneration/degeneration cycles until the muscle fibers lose that capacity and will be replaced by fibrous or fatty tissue. Treatment with resveratrol aims to increase the expression of the peroxisome proliferator-activated receptor-gamma coactivator (PGC-1α)-1 alpha, a transcriptional coactivator that targets the utrophin gene, a protein capable of taking the place of dystrophin. Gordon (2013) confirms the increase in utrophin mRNA and also indicated that there was a reduction in total immune cell infiltration, decreasing inflammation.

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by the selective loss of motor neurons in the brain and spinal cord causing muscle weakness and atrophy, spasms, paralysis, and respiratory failure until death (Mancuso et al. 2014). The causes of this pathology are mutations in SOD1, which causes the accumulation of free radicals; there is also an excessive accumulation of glutamate in the synapse that can kill neurons; in addition, there is an increase in the amount of free metals such as Cu, Zn, and Ca which generates oxidative stress; neurons also have mitochondrial dysfunction by the presence of vacuoles in them. Tellone et al. (2014) report that treating ALS with resveratrol, a favorable effect is obtained, resveratrol will activate STIR1 transcription factor that will deacetylate heat shock factor (HSF1) which reduces the death of neurons; in addition to this activation, cell death factor p53 is inhibited by increasing the expression of pro-apoptotic factors such as Bax. In addition to this, resveratrol activates PGC-1α by activating STIR1, which favors the formation of mitochondria and improves cellular respiration due to the induction of nuclear respiration factors (NRF) 1 and 2.

9.5 Bioavailability and Metabolism of Resveratrol

The recent attention for this compound is expanded by several epidemiological studies that demonstrate an inverse relationship among balanced consumption of different food as wines, peanuts, and select teas, especially for several disease applications (Chimento et al. 2019). Numerous studies have investigated the absorption, transport, and metabolism of resveratrol in vitro and ex vivo. Upon ingestion, resveratrol or its precursors go through the gastrointestinal tract, and it is estimated that around 70–75% of the intake of resveratrol is absorbed (Chaplin et al. 2018). Almost several resveratrol and derived metabolites have been described in animal or human plasma, urine, and various tissues, mostly generated by three major pathways: hepatic and intestinal glucuronidation, hepatic and intestinal sulfation, and gut microbial transformation (Luca et al. 2020). Initially, absorption of resveratrol was evaluated using isolated rat small intestine perfusion models, but other studies were employed about glucuronidation (G), and sulfation (S) in the duodenum was used to establish as comparative models as hepatic cells (Wenzel and Somoza 2005).

The biochemical structure of resveratrol conducts low water solubility (<0.05 mg/mL), which influences its absorption. On the other hand, to increase its solubility, require ethanol or organic solvents (Gambini et al. 2015). Resveratrol also demonstrated its ability to generate organic molecular complexes; these bioactives can be taken up by the intestine as xenobiotics and consequently cross the intestinal epithelium to the blood via a transcellular pathway; this route takes place through the enterocytes in the small intestine. Enterocytes are the first site of reported resveratrol metabolism after being internalized by either passive diffusion (Springer and Moco 2019). After absorption, resveratrol suffers serious and quick metabolization. It is essential to reference that no phase I reactions of resveratrol, such as oxidation, reductions, or hydrolyzes, were observed in the human systems (Wenzel and Somoza 2005). Once resveratrol is absorbed into the enterocyte, it undergoes phase II reactions of drug metabolism, producing polar metabolites, with simpler excretion in the body.

Resveratrol conjugation with sulfate was mediated by sulfotransferases (SULTs) and with glucuronate by uridine 5′-diphospho-glucuronosyltransferases (UGTs) (Springer and Moco 2019); on the other hand, intestinal bacteria also contribute to resveratrol metabolism, having the ability to convert it via hydrogenation to dihydroresveratrol (DHR), which is partly absorbed and further metabolized to conjugated forms (monosulfate DHR, monoglucuronide DHR) that can easily be eliminated in urine (Luca et al. 2020). The family of SULTs demonstrates a broad spectrum of diverse endogenous and exogenous substrate activity (1A1, 1A2, 1A3, and 1E1) and generates resveratrol-3′-*O*-sulfate (R3S), resveratrol-4′-*O*-sulfate (R4S), and resveratrol disulfates (RdS) as metabolite result by the sulfate group to a hydroxyl group in phenolic compounds. On the other hand, the UGTs are a large family of related enzymes involved on detoxification, which activity (1A1,1A9, 1A3, 1A6, 1A7, 1A8, and 1A10) catalyzes the conjugation of resveratrol with glucuronic acid, yielding principally resveratrol-3′-*O*-glucuronide (R3G) and

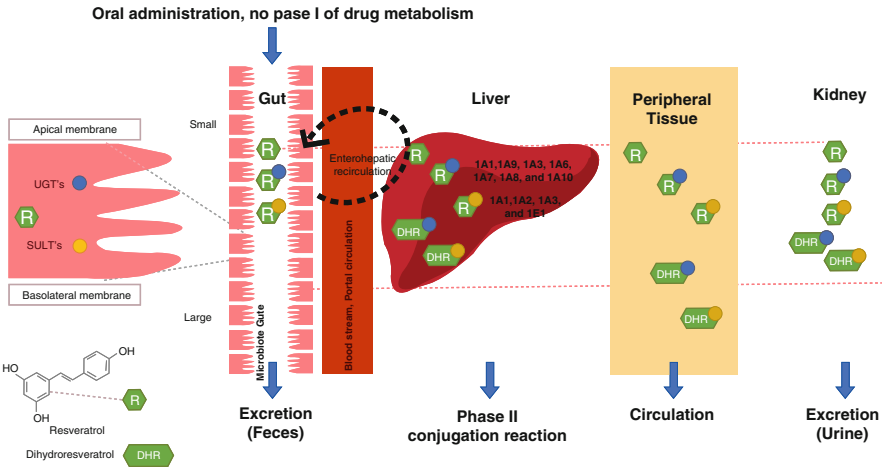

Fig. 9.2 Bioavailability and metabolism of resveratrol

resveratrol-4′-*O*-glucuronide (R4G) (Wang and Sang 2018). Figure 9.2 represented the metabolic fate and biotransformed resveratrol in the human gastrointestinal tract and metabolism in different organs. After conjugation, resveratrol sulfates and glucuronides have two possible fates; they can be transported through the apical membrane and extent the intestinal lumen, or they can pass through the basolateral membrane and enter the bloodstream. On both membranes, the enterocyte presents ABC (ATP-binding cassette) transporters, which are part of a large family of transport proteins that are considered instrumental in drug absorption and response diffusion (Springer and Moco 2019). On the apical and basolateral membrane, transporters are not limited to represent a role in the absorption and distribution of resveratrol metabolites in the small intestine (when resveratrol or his metabolites extent the bloodstream, they can be transferred by binding to blood proteins such as hemoglobin, albumin, and lipoproteins) as they are also expressed in several tissues, such as the liver or kidneys. Resveratrol demonstrate a high degree of lipophilicity; cant circulates single in plasma, required to binding proteins, such as albumins or low-density lipoproteins (LDL), occurs in a great extent (up to 90% of free resveratrol). However, despite being mostly bound to serum proteins, hepatic uptake is still efficient, the liver being considered the primary accumulation site of resveratrol and its metabolites (Gambini et al. 2015). Resveratrol is principally excreted in urine and feces. Total elimination after oral administration of ^{14}C-labeled resveratrol in humans was demonstrated around 70 to 98%, which is 53–85% in urine and 3.3–35% in feces. In urine, metabolites are considered 22–44% of the ingested dose, with 11–31% sulfate conjugates and 9–16% glucuronides (Walle et al. 2004; Tome-Carneiro et al. 2013).

The resveratrol oral administration is the ideal method for treatments in humans; it is known that plasma absorption of the unchanged resveratrol depends on the dosages consumed. Preclinical investigations elucidate the appropriate resveratrol

oral dosage and bioavailability by human patients. Several studies demonstrated an oral dose of 25 mg of resveratrol, presented in plasma concentration around 1–5 ng/mL of resveratrol (Chimento et al. 2019). Administration of higher dosages (up to 5 g) indicated the increase in the intensity of unchanged resveratrol up to 530 ng/mL, demonstrating how, after a high resveratrol dosage, only a low quantity of the unchanged resveratrol is present in the plasma. Even if resveratrol seems like to be well-accepted, tolerated, and safe, administration of higher oral doses does not consent to improve therapeutic effects, but, as an alternative, perhaps the cause of the side effects seen at the dose of 1 g/kg (body weight) including diarrhea, abdominal pain, and nausea.

Consequently, based on the findings from clinical studies, it appears that the main obstacle that must be overcome to consider resveratrol as a therapeutic agent is its low bioavailability (Boocock et al. 2007; Almeida et al. 2009; Patel et al. 2011). Wenzel and Somoza in 2005 conclude that resveratrol, in human patients, whether as aglycone or in its glycosidic form, is also absorbed quite fast after oral consumption and resveratrol levels were readily measurable in plasma and urine with the highest level plasma concentrations around 30 to 60 min after ingestion.

In the present day, scientific resveratrol investigation in the world consists of around 140 clinical trials in humans by disease treatments (clinicaltrials.gov), and more than 10,000 scientific papers consist of realizing an effort to elucidate different employs, uses, and effects of resveratrol. Due to differing doses, disparate experimental setups, low statistical power, and a myriad of biological or other types of confounders, the fate and effect of resveratrol in humans remain indefinable. Mechanisms of action are diverse and of potential use for obesity, cardiovascular health, inflammation, metabolic health, antioxidant activity, and cancer management. Therefore, resveratrol is of wide pleiotropy. Systems conducted approaches that help map the impacts of multitargeted compounds such as resveratrol and emphasize links among phase II metabolism, redox pathways, and bioenergetics, linked by protein targets regulated by resveratrol (Springer and Moco 2019).

However, despite these factual scientific data, the resveratrol paradox (defined as low bioavailability and high bioactivity) still raises serious questions, as the final responsible mechanisms incriminated for the observed effects have not yet been elucidated. Since oral bioavailability is mainly dependent on aqueous solubility, membrane permeability, and metabolic stability, these factors are further addressed below to assess its problematic bioavailability. Despite the advances, the scientific community still has yet to continue with efforts to conduct more extensive and more deeply characterized studies which could be an aim of the research community in order to bridge the current gaps in knowledge on resveratrol metabolism and beneficial effects.

9.6 Therapy Resveratrol Carriers

Resveratrol, as described, is a well-studied natural compound with great therapeutic potential (Wiciński et al. 2020). Despite promising results, the widespread use of resveratrol has had limited success, largely due to its instability, low bioavailability

and solubility, as well as insufficient systemic administration (Soo et al. 2016). Two geometric isomers of resveratrol are known: *trans* and c*is*. Both isomers often exist in combination. The *trans* form is more biologically active, and this isomer can become *cis* under ultraviolet light. Resveratrol is characterized by low half-life (less than 0.25 h). So, for its proper action, it is difficult to ensure the therapeutic concentration. Previous in vitro studies have shown that 5μmol/L (Sessa et al. 2014) resveratrol is the minimum concentration required to achieve its chemopreventive effects. It is known that 75% of resveratrol is possibly absorbed by transepithelial diffusion under oral administration in humans. However, due to the rapid and extensive metabolism in the intestine and liver, oral bioavailability is low (<1%) (Christakis Sergides et al. 2016). The drug suffers enterohepatic recirculation and extensive first-pass metabolism by CYP3A4 in the liver, resulting in very low bioavailability. Oral administration of repeated or increased doses does not improve compound levels. The pharmacokinetics of resveratrol have shown a circadian variation, with greater bioavailability after morning administration (Christakis Sergides et al. 2016).

Resveratrol glucuronides and sulfates are the main metabolites detected in urine and plasma, in addition to reduced dihydro-resveratrol conjugates and other unknown highly polar products (Pecyna et al. 2020). In addition to metabolites generated in the liver and intestine, the impact on resveratrol transformation can be assigned to colonic bacterial activity (dos Santos et al. 2019). By controlling the activity of β-glucuronidase and sulfatase enzymes, the efficacy of resveratrol at the target site can be improved by tissue-specific accumulation of resveratrol (Lu et al. 2013; Pecyna et al. 2020).

Lu et al. (2009) propose the administration of resveratrol in a stable form conjugated with sulfate, achieving the generation of parent compound gradually for the beneficial effects in vivo. The activities of resveratrol metabolites were also demonstrated, these being pharmacologically active in vivo (Kiskova et al. 2020).

So, pharmacokinetic properties of resveratrol such as low solubility, rapid degradation, and extensive metabolism are known. This translates into insufficient bioavailability in its oral application. Furthermore, it is known that under exposure to light, trans-resveratrol, the biologically active isomer, is rapidly converted to cis-resveratrol (Singh et al. 2014). This presents several problems for the application of resveratrol in therapy that can be solved by such strategies as the co-administration of enzymatic inhibitors of metabolism, the synthesis and use of its analogues, as well as the design of new administration systems (Silva et al. 2014). Moreover, to overcome the described physicochemical and pharmacokinetic restrictions, nanotechnology presents a powerful strategy considering the nanoencapsulation of resveratrol (Wang et al. 2011; Soo et al. 2016). Nanotechnology makes it possible to obtain nanoparticles loaded with biologically active compounds. The use of nanoparticles was approved by the United States Food and Drug Administration (FDA) in 1983. The particles are normally classified according to their size: normally the diameter of nanoparticles loaded with resveratrol is less than 1000 nm, and only in some cases is the diameter of ultrafine particles less than 100 nm (Ansari et al. 2011; Keservani et al. 2017).

The nanoencapsulation of this bioactive natural compound as one of the chemotherapeutic agents provides many advantages in control of degradation and in the interaction with biological systems, as well as improvement in bioavailability, retention time, absorption, and intratissue and intracellular penetration (Penalva et al. 2015; Sharma et al. 2018). Several nanoformulations focused on enhancing therapeutic potential of resveratrol have been developed Keservani et al. 2021) (Table 9.2).

Initially, the nanoencapsulation of resveratrol was performed using chitosan nanoparticles. However, the release of resveratrol was limited in the presence of solidifying agents (Kiskova et al. 2020).

Nanosystems with biocompatible and biodegradable polymers have been applied for resveratrol entrapment (Sanna et al. 2013). These systems made it possible to improve the solubilization of the drug and protect it from degradation. Moreover, different systems of nanoparticles loaded with resveratrol cause a greater effect on the viability of cancer cells even in lower doses than free resveratrol (Table 9.2), mediated by the discrepancy of intracellular reactive oxygen species. Often times, nanocarriers coated with poly (ethylene glycol) (PEG) on their surface as well as mPEG-poly(caprolactone)-based nanoparticles allowed compound accumulation in tumors through the enhanced effect of permeability and retention (Wang et al. 2011; Sanna et al. 2013) (Table 9.2).

Resveratrol-loaded nanoparticles protected cells from damage induced by beta-amyloid peptide (Abeta) in a dose-dependent manner by attenuating intracellular oxidative stress and caspase-3 activity (Lu et al. 2009, 2012) (Table 9.2). Solid lipid nanoparticles (SLN) with a size smaller than 180 nm showed the ability to quickly cross the cell membrane, were distributed throughout the cytosol and moved successively between different cell levels, and were located in the perinuclear region without inducing cytotoxicity. Moreover, in these nanocarriers, solubility, stability, and intracellular delivery were all increased by loading into SLN (Shidhaye et al. 2008; Pandita et al. 2014).

In vitro assays revealed that liposome-encapsulated curcumin and resveratrol successfully inhibited cell growth and induced apoptosis by inhibition of phosphatase and tensin homolog (PTEN), including p-Akt, cyclin D1, mammalian rapamycin, and RA (Narayanan et al. 2009).

All studied nanocarriers are suitable to be used for the delivery of bioactive resveratrol (Table 9.2). The encapsulation of resveratrol in polymeric nanoparticles allows the optimization of its charge, an effective controlled release, and protection against transformation by exposure to light, which opens new perspectives for its use in (nano) chemoprevention/chemotherapy. Thus, solid lipid nanoparticles and nanostructured lipid carriers enhance the oral bioavailability of resveratrol (Gokce et al. 2012; Jose et al. 2014).

The anticancer activity and the molecular mechanism of subcutaneously implanted human ovarian primary carcinoma cells in nude mice were demonstrated for resveratrol-bovine serum albumin nanoparticles. The growth of carcinomas was inhibited to a greater degree when compared to free resveratrol due to the mitochondrial apoptotic pathway activated by applied treatment (Neves et al. 2013). An

Table 9.2 Nanoformulations for resveratrol delivery to enhance its therapeutic effect

Delivery system	Characteristics	References
Poly(lactide) (PLA) nanoparticles	Resveratrol-loaded polysorbate 80-coated poly(lactide) nanoparticles (but not free resveratrol) demonstrated neuroprotective effect in mice with induced Parkinson's disease	Da Rocha et al. (2015)
Poly-(lactic-co-glycolic) acid (PLGA) nanoparticles	Transferrin-conjugated polyethylene glycol-polylactic acid nanoparticles conjugated with resveratrol showed a therapeutic effect for glioma	Guo et al. (2013)
Poly(epsilon-caprolactone) (PCL) nanoparticles	Nanosystems, composed of a biocompatible blend of poly(epsilon-caprolactone) and poly (D,L-lactic-*co*-glycolic acid)-poly(ethylene glycol) conjugate, had antiproliferative efficacy on prostate cancer cells	Sanna et al. (2013)
Polymeric micelles	Resveratrol-loaded polymeric micelles basing on amphiphilic block copolymer protected PC12 cells from Abeta-induced damage in a dose-dependent manner by attenuating intracellular oxidative stress and caspase-3 activity	Lu et al. (2009)
Nanoparticles based on zein, an amphiphilic protein	Zein-based nanoparticles provided high and prolonged plasma levels of the polyphenol, increase in oral bioavailability of resveratrol, decrease of the endotoxic symptoms in mice treated with LPS, decrease in serum tumor necrosis factor-alpha (TNF-α) in comparison with control	Penalva et al. (2015)
Lecithin-based nanoemulsions	Lecithin-based nanoemulsions were able to transport resveratrol through cell monolayers in characteristically shorter times (1–6 h) than those required for their metabolization (3–12 h), allowing for better preservation of the integrity of the emulsion droplets, protecting the resveratrol against chemical degradation, providing the capability of nanoemulsions in sustained release of resveratrol	Sessa et al. (2014)
Cyclodextrins	Betta cyclodextrin-based nanosponges were obtained for buccal delivery and topical application by hyper-cross-linked cyclodextrin polymers with carbonyldiimidazole forming three-dimensional systems. Formulation increased resveratrol solubility, cytotoxicity against HCPC-I cells, permeation in pigskin, and accumulation in rabbit mucosa. Resveratrol solubility was improved by the formation of inclusion complexes with hydropropyl-cyclodextrins and micellar systems. Stable resveratrol system was achieved to incorporate it in the food and pharmaceutical products.	Ansari et al. (2011) Silva et al. (2014) Venuti et al. (2014)

(continued)

Table 9.2 (continued)

Delivery system	Characteristics	References
	Resveratrol/sulfobutylether-β-cyclodextrin inclusion complex was obtained with high affinity for resveratrol with molar ratio 1:1 and high stability	
Liposomes	Resveratrol was stablished in formulations obtained by reverse-phase evaporation method with or without poly (ethylene glycol-2000)—grafted distearoyl phosphatidylethanolamine. Resveratrol-loaded liposomes improve anticancer effect A conjugate of dequalinium polyethylene glycol-distearoylphosphatidylethanolamine with resveratrol was obtained as a complex targeting mitochondria. The complex was considered a potential treatment for lung cancers that induces apoptosis through the mitochondrial signaling pathway	Lu et al. (2012) Wang et al. (2011)
Dual nanoencapsulation in cyclodextrin inside liposomes	Resveratrol was encapsulated in cyclodextrin inclusion complexes in the lipophilic and hydrophilic compartments of the liposomes as an example of a dual carrier system	Soo et al. (2016)
Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs)	Solid lipid nanoparticles (SLN) and resveratrol-loaded nanostructured lipid carriers (NLC) were obtained by a modified hot homogenization technique. In vitro resveratrol remained associated with lipid nanoparticles after incubation in digestive fluids for several hours Resveratrol-coated stearic acid-based SLNs coated with poloxamer 188 were obtained by the solvent diffusion and solvent evaporation method. The lipid formulation improved at 8.035-fold the oral bioavailability of resveratrol compared to suspension of the drug	Neves et al. (2013) Pandita et al. (2014)

antiglioma effect was observed in the presence of trans-resveratrol-loaded lipid core nanocapsules in vitro and in vivo. A greater decrease in the viability of C6 glioma cells was observed with encapsulated than free resveratrol, without toxicity to healthy neural cells. The treatment caused apoptotic cell death through early arrest in the S and G1 phases of the cell cycle. This treatment led to a marked decrease in tumor size and reduced the incidence of some features associated with malignant tumors compared to resveratrol in solution in vivo (Guo et al. 2013).

Resveratrol-loaded nanoparticles based on poly(e-caprolactone) and poly(D, L-lactic-co-glycolic acid)-poly(ethylene glycol) were used for prostate cancer treatment. Resveratrol released under simulation from gastrointestinal fluids was 55% resveratrol in the first 2 h in an acid medium and reached 100% in the next 5 h at

pH 7.4. Confocal microscopy revealed that CaP cell lines efficiently absorbed these nanoparticles. Treatment of androgen-independent and hormone-sensitive prostate cancer cells was more efficient in nanosystem than free resveratrol (Sanna et al. 2013).

Resveratrol chemopreventive effect was observed as its ability to counteract CSC-induced DNA fragmentation and to activate protective apoptosis in bronchial epithelial cells in both in vitro and ex vivo experiments. Nanoparticles reduced the toxicity of resveratrol and increased its ability to counteract the cytotoxicity of CSC (Da Rocha et al. 2015; Beloqui et al. 2016).

Resveratrol is a suitable treatment for chemoprevention and is a viable option for the control of cancer in the early stages of the carcinogenesis process and also in other degenerative diseases. To take advantage of the beneficial therapeutic potential, pharmacokinetic problems are solved using resveratrol prodrugs and nanostructured delivery systems. The use of the latter leads to improvement in bioavailability, intracellular penetration, and control of administration, as well as protection against degradation and reduction of potential toxicity. Currently, studies are being developed to approve the use of resveratrol-based nanosystems in clinical practice, which will drive the evolution of innovative nanodevices capable of consolidating the chemopreventive potential of resveratrol.

9.7 Conclusions

The biological effects reported from the studies of resveratrol have shown that it is a molecule with an important capacity to generate effects in diverse mechanisms of action of a great variety of cellular models in vitro and in experimental models in vivo. All these studies reveal the importance of this molecule as a target for treatment and even prevention of various diseases that currently exist, such as metabolic, degenerative, cardiovascular, inflammatory, carcinogenic, and neurological diseases and even infections by etiological agents such as viruses and bacteria.

Scientific evidence indicates that the main effects they generate in tumor cells, diseased or infected cells, are related to the chemical and immunological sensitization that it causes, activating different signaling pathways and molecular mechanisms that favor the therapeutic response, even activating the cells themselves of the host to generate the immunological effect. Some of these mechanisms occur through inflammatory processes, activating cells of innate and adaptive immunity to promote their maturation and act as effector cells. In addition, it can stimulate the secretion of pro-inflammatory cytokines, promote apoptosis, activate lipid and carbohydrate metabolism, and even trigger specific responses through the expression of specific proteins and the activation of genes.

All these promising effects of resveratrol place this molecule of natural origin as one of the most promising nutraceuticals for the treatment of various pathologies, having the advantage that being a molecule of natural origin, its bioavailability in nature allows it to be easy access for consumption. However, more studies will

always be necessary to further understand the mechanisms on in vivo trials and even clinical trials of resveratrol, since there are also reports of antagonistic effects of resveratrol, and this could influence the desired effects in conjunction with physiological conditions of the organisms in which it is evaluated.

Acknowledgments A special thanks to the Research and Postgraduate Department of the Autonomous University of Coahuila (UAdeC). Also a special thanks to the Laboratorio Nacional BIOBANCO CONACYT (LANBIOBAN) of UAdeC/UANL.

Conflicts of Interest The authors declare no conflict of interest.

References

Abba Y, Hassim H, Hamzah H, Noordin MM (2015) Antiviral activity of resveratrol against human and animal viruses. Adv Virol 2015:1–7

Ahmed T, Javed S, Javed S et al (2016) Resveratrol and Alzheimer's disease: mechanistic insights. Mol Neurobiol 54:2622–2635

Ajith Y, Dimri U, Dixit SK et al (2017) Immunomodulatory basis of antioxidant therapy and its future prospects: an appraisal. Inflammopharmacology 25:487–498

Almeida L, Vaz-da-Silva M, Falcão A et al (2009) Pharmacokinetic and safety profile of trans-resveratrol in a rising multiple-dose study in healthy volunteers. Mol Nutr Food Res 53:7–15

Annunziata G, Maisto M, Schisano C et al (2018) Resveratrol as a novel anti-herpes simplex virus nutraceutical agent: an overview. Viruses 10:473–483

Ansari KA, Vavia PR, Trotta F et al (2011) Cyclodextrin-based nanosponges for delivery of resveratrol: *in vitro* characterization, stability, cytotoxicity and permeation study. AAPS J Am Assoc Pharmaceut Scientists 12:279–286

Asati V, Mahapatra DK, Bharti SK (2016) PI3K/Akt/mTOR and Ras/Raf/MEK/ERK signaling pathways inhibitors as anticancer agents: structural and pharmacological perspectives. Eur J Med Chem 109:314–341

Banez MJ, Geluz MI, Chandra A et al (2020) A systemic review on the antioxidant and anti-inflammatory effects of resveratrol, curcumin, and dietary nitric oxide supplementation on human cardiovascular health. Nutr Res 78:11–26

Bastianetto S, Ménard C, Quirion R (2015) Neuroprotective action of resveratrol. Biochim Biophys Acta (BBA) - Mol Basis Dis 1852:1195–1201

Baur JA, Pearson KJ, Price NL et al (2006) Resveratrol improves health and survival of mice on a high-calorie diet. Nature 444:337–342

Beloqui A, Solinis MA, Rodriguez-Gascon A et al (2016) Nanostructured lipid carriers: promising drug delivery systems for future clinics. Nanomedicine 12:143–161

Berman A, Motechin R, Wiesenfeld M et al (2017) The therapeutic potential of resveratrol: a review of clinical trials. NPJ Precision Oncol 1:1–9

Bhatt SR, Lokhandwala MF, Banday AA (2011) Resveratrol prevents endothelial nitric oxide synthase uncoupling and attenuates development of hypertension in spontaneously hypertensive rats. Eur J Pharmacol 667:258–264

Bishayee A, Barnes KF, Bhatia D et al (2010) Resveratrol suppresses oxidative stress and inflammatory response in diethylnitrosamine-initiated rat hepatocarcinogenesis. Cancer Prev Res 3:753–763

Boehncke W-H (2015) Etiology and pathogenesis of psoriasis. Rheum Dis Clin 41:665–675

Boocock DJ, Faust GES, Patel KR et al (2007) Phase I dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemopreventive agent. Cancer Epidemiol Biomark Prev 16:1246–1252

Borge AM, Solano MV, Valverde JPS (2013) El resveratrol y sus posibles usos como nueva terapia farmacológica. Rev Méd Costa Rica Centro América LXX 608:679–684

Buhrmann C, Shayan P, Goel A, Shakibaei M (2017) Resveratrol regulates colorectal cancer cell invasion by modulation of focal adhesion molecules. Nutrients 9:1073–1095

Calvo M, Corral P, Lopez G et al (2017) El resveratrol protege contra la respuesta inflamatoria en páncreas secundaria al envejecimiento. Rev Complutense Ciencias Veterinarias 11:216–221

Cao X, Luo T, Luo X, Tang Z (2014) Resveratrol prevents AngII-induced hypertension via AMPK activation and RhoA/ROCK suppression in mice. Hypertens Res 37:803–810

Catalogna G, Moraca F, D'Antona L et al (2019) Review about the multi-target profile of resveratrol and its implication in the SGK1 inhibition. Eur J Med Chem 183:111675

Chai R, Fu H, Zheng Z et al (2017) Resveratrol inhibits proliferation and migration through SIRT1 mediated post-translational modification of PI3K/AKT signaling in hepatocellular carcinoma cells. Mol Med Rep 16:8037–8044

Chang C, Chang C, Huang J, Hung L (2012) Effect of resveratrol on oxidative and inflammatory stress in liver and spleen of streptozotocin-induced type 1 diabetic rats. Chin J Physiol 55:192–201

Chaplin A, Carpéné C, Mercader J (2018) Resveratrol, metabolic syndrome, and gut microbiota. Nutrients 10:1–29

Chen X, Qiao H, Liu T et al (2012) Inhibition of herpes simplex virus infection by oligomeric stilbenoids through ROS generation. Antivir Res 95:30–36

Chen J, Cao X, Cui Y et al (2018) Resveratrol alleviates lysophosphatidylcholine-induced damage and inflammation in vascular endothelial cells. Mol Med Rep 17:4011–4018

Chimento A, De Amicis F, Sirianni R et al (2019) Progress to improve oral bioavailability and beneficial effects of resveratrol. Int J Mol Sci 20:1381

Choi AMK, Ryter SW, Levine B (2013) Mechanisms of disease: autophagy in human health and disease. N Engl J Med 368:651–662

Christakis Sergides C, Chirilă M, Silvestro L et al (2016) Bioavailability and safety study of resveratrol 500 mg tablets in healthy male and female volunteers. Exp Ther Med 11(1):164–170

Chun YH, Park JY, Lee H et al (2013) Rhinovirus-infected epithelial cells produce more IL-8 and rantes compared with other respiratory viruses. Allergy, Asthma Immunol Res 5:216–223

Civitarese AE, Carling S, Heilbronn LK et al (2007) Calorie restriction increases muscle mitochondrial biogenesis in healthy humans. PLoS Med 4:e76

Da Rocha LG, Bonfanti Santos D, Colle D et al (2015) Improved neuroprotective effects of resveratrol-loaded polysorbate 80-coated poly(lactide) nanoparticles in MPTP-induced parkinsonism. Nanomedicine (Lond) 10:1127–1138

De Ligt M, Timmers S, Schrauwen P (2015) Resveratrol and obesity: can resveratrol relieve metabolic disturbances? Biochim Biophys Acta (BBA) - Mol Basis Dis 1852:1137–1144

de Oliveira ALB, Monteiro VVS, Navegantes-Lima KC et al (2017) Resveratrol role in autoimmune disease—a mini-review. Nutrients 9:1306

De Sá-Coutinho D, Pacheco M, Frozza R et al (2018) Anti-inflammatory effects of resveratrol: mechanistic insights. Int J Mol Sci 19:1812–1837

Dolinsky VW, Chakrabarti S, Pereira TJ et al (2013) Resveratrol prevents hypertension and cardiac hypertrophy in hypertensive rats and mice. Biochim Biophys Acta Mol basis Dis 1832:1723–1733

Dos Santos AS, Rodrigues de Albuquerque TM, de Brito Alves JL et al (2019) Effects of quercetin and resveratrol on *in vitro* properties related to the functionality of potentially probiotic *Lactobacillus* strains. Front Microbiol 10:2229–2231

Dudek SE, Wixler L, Nordhoff C et al (2011) The influenza virus PB1-F2 protein has interferon-antagonistic activity. Biol Chem 392:1135–1144

Elmali N, Baysal O, Harma A et al (2007) Effects of resveratrol in inflammatory arthritis. Inflammation 30:1–6
Espinoza JL, Takami A, Trung LQ et al (2012) Resveratrol prevents EBV transformation and inhibits the outgrowth of EBV-immortalized human B cells. PLoS One 7:e513061–e513067
Faith SA, Sweet TJ, Bailey E et al (2006) Resveratrol suppresses nuclear factor-κB in herpes simplex virus infected cells. Antivir Res 72:242–251
Fan Y, Chiu JF, Liu J et al (2018) Resveratrol induces autophagy-dependent apoptosis in HL-60 cells. BMC Cancer 18:1–10
Feng Y, Jiang X, Ma F et al (2018) Resveratrol prevents osteoporosis by upregulating FoxO1 transcriptional activity. Int J Mol Med 41:202–212
Figueira L, González J (2018) Efecto del resveratrol sobre las concentraciones séricas del factor de crecimiento endotelial vascular durante la aterosclerosis. Clín Investig Arteriosclerosis 30(5): 209–216
Firestein GS, McInnes IB (2017) Immunopathogenesis of rheumatoid arthritis. Immunity 46:183–196
Fruh SM (2017) Obesity: risk factors, complications, and strategies for sustainable long-term weight management. J Am Assoc Nurse Pract 29:S3–S14
Fu Y, Chung F-L (2018) Oxidative stress and hepatocarcinogenesis. Hepatoma Res 4:39–50
Fu S, Lv R, Wang L et al (2018) Resveratrol, an antioxidant, protects spinal cord injury in rats by suppressing MAPK pathway. Saudi J Biol Sci 25:259–266
Gambini J, López-Grueso R, Olaso-González G et al (2013) Resveratrol: distribución, propiedades y perspectivas. Rev Esp Geriatr Gerontol 48(2):79–88
Gambini J, Inglés M, Olaso G et al (2015) Properties of resveratrol: in vitro and in vivo studies about metabolism, bioavailability, and biological effects in animal models and humans. Oxidative Med Cell Longev 2015:1–13
Gokce EH, Korkmaz E, Dellera E et al (2012) Resveratrol-loaded solid lipid nanoparticles *versus* nanostructured lipid carriers: evaluation of antioxidant potential for dermal applications. Int J Nanomedicine 7:1841–1850
Gordon B, Delgado D, Kostek M (2013) Resveratrol decreases inflammation and increases utrophin gene expression in the mdx mouse model of duchenne muscular dystrophy. Clin Nutr 32(1): 104–111
Grujic-Milanovic J, Miloradovic Z, Jovovic D et al (2017) The red wine polyphenol, resveratrol improves hemodynamics, oxidative defence and aortal structure in essential and malignant hypertension. J Funct Foods 34:266–276
Guo W, Li A, Jia Z et al (2013) Transferrin modified PEG-PLA-resveratrol conjugates: *in vitro* and *in vivo* studies for glioma. Eur J Pharmacol 718:41–47
Hanrui Z, Jing Z, Zoltan U, Cuihua Z (2009) Resveratrol improves endothelial function. Arterioscler Thromb Vasc Biol 29:1164–1171
Hara Y, Torii R, Ueda S et al (2018) Inhibition of tumor formation and metastasis by a monoclonal antibody against lymphatic vessel endothelial hyaluronan receptor 1. Cancer Sci 109:3171–3182
Heo JR, Kim SM, Hwang KA et al (2018) Resveratrol induced reactive oxygen species and endoplasmic reticulum stress-mediated apoptosis, and cell cycle arrest in the A375SM malignant melanoma cell line. Int J Mol Med 42:1427–1435
Howitz KT, Bitterman KJ, Cohen HY et al (2003) Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. Nature 425:191–196
Huang D-D, Shi G, Jiang Y et al (2020) A review on the potential of resveratrol in prevention and therapy of diabetes and diabetic complications. Biomed Pharmacother 125:109767
Inglés M, Gambini J, Miguel MG et al (2014) PTEN mediates the antioxidant effect of resveratrol at nutritionally relevant concentrations. Biomed Research International
Iwai A, Shiozaki T, Kawai T et al (2010) Influenza A virus polymerase inhibits type I interferon induction by binding to interferon β promoter stimulator 1. J Biol Chem 285:32064–32074

Jang M, Cai L, Udeani GO et al (1997) Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science 275:218–220
Jiang N, Dai Q, Su X et al (2020) Role of PI3K/AKT pathway in cancer: the framework of malignant behavior. In: Molecular biology reports. Springer, Cham, pp 4587–4629
Jose S, Anju SS, Cinu TA et al (2014) *In vivo* pharmacokinetics and biodistribution of resveratrol-loaded solid lipid nanoparticles for brain delivery. Int J Pharm 474:6–13
Juan ME, Wenzel U, Daniel H, Planas JM (2008) Resveratrol induces apoptosis through ROS-dependent mitochondria pathway in HT-29 human colorectal carcinoma cells. J Agric Food Chem 56:4813–4818
Keservani RK, Kesharwani RK, Sharma AK (2017) Introduction to nanotechnology in drug delivery. In: Drug delivery approaches and nanosystems. Apple Academic, pp 1–19. ISBN: 9781771885836
Keservani RK, Kesharwani RK, Sharma AK (2021) Nutraceuticals. In: Enhancing the therapeutic efficacy of herbal formulations. IGI Global, pp 241–266. ISBN13: 9781799844532
Kesharwani RK, Misra K (2010) Prediction of binding site for curcuminoids at human topoisomerase II α protein; an in silico approach. Curr Sci 101(8):1060–1064
Killip MJ, Fodor E, Randall RE (2015) Influenza virus activation of the interferon system. Virus Res 209:11–22
Kimura Y, Sumiyoshi M (2016) Resveratrol prevents tumor growth and metastasis by inhibiting lymphangiogenesis and M2 macrophage activation and differentiation in tumor-associated macrophages. Nutr Cancer 68:667–678
Kiskova T, Kubatka P, Büsselberg D et al (2020) The plant-derived compound resveratrol in brain cancer: a review. Biomol Ther 10(1):161–164
Kjær TN, Thorsen K, Jessen N et al (2015) Resveratrol ameliorates imiquimod-induced psoriasis-like skin inflammation in mice. PLoS One 10:e0126599
Ko JH, Sethi G, Um JY et al (2017) The role of resveratrol in cancer therapy. Int J Mol Sci 18:1–36
Kong D, Chen F, Sima N (2015) Inhibition of focal adhesion kinase induces apoptosis in bladder cancer cells via Src and the phosphatidylinositol 3-kinase/Akt pathway. Exp Ther Med 10: 1725–1731
Krawiec M, Westcott J, Hong WC et al (2001) Persistent wheezing in very young preschool children reflects lower respiratory inflammation. Am J Respir Crit Care Med 163:1290–1291
Kuršvietienė L, Stanevičienė I, Mongirdienė A, Bernatonienė J (2016) Multiplicity of effects and health benefits of resveratrol. Medicina 52:148–155
Lagouge M, Argmann C, Gerhart-Hines Z et al (2006) Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1α. Cell 127:1109–1122
Lançon A, Frazzi R, Latruffe N (2016) Anti-oxidant, anti-inflammatory and anti-angiogenic properties of resveratrol in ocular diseases. Molecules 21(3):304
Larrosa M, García-Conesa MT, Espín JC, Tomás-Barberán FA (2010) Ellagitannins, ellagic acid and vascular health. Mol Asp Med 31:513–539
Latruffe N, Lançon A, Limagne E et al (2014) Bioreactivity of resveratrol toward inflammation processes. Recent advances in redox active plant and microbial products, pp 193–207
Latruffe N, Lancon A, Frazzi R et al (2015) Exploring new ways of regulation by resveratrol involving miRNAs, with emphasis on inflammation. Ann NY Acad Sci 1348:97–106
Lau SKP, Lau CCY, Chan KH et al (2013) Delayed induction of proinflammatory cytokines and suppression of innate antiviral response by the novel Middle East respiratory syndrome coronavirus: implications for pathogenesis and treatment. J Gen Virol 94:2679–2690
Lee M, Kim S, Kwon O et al (2009a) Anti-inflammatory and anti-asthmatic effects of resveratrol, a polyphenolic stilbene, in a mouse model of allergic asthma. Int Immunopharmacol 4:418–424
Lee JH, Song MY, Song EK et al (2009b) Overexpression of SIRT1 protects pancreatic β-cells against cytokine toxicity by suppressing the nuclear factor-κB signaling pathway. Diabetes 58: 344–351
Lee S-M, Yang H, Tartar DM et al (2011) Prevention and treatment of diabetes with resveratrol in a non-obese mouse model of type 1 diabetes. Diabetologia 54:1136–1146

Lee JH, Kim JS, Park SY, Lee YJ (2016) Resveratrol induces human keratinocyte damage via the activation of class III histone deacetylase, Sirt1. Oncol Rep 35:524–529
Li S, Zhao G, Chen L et al (2016) Resveratrol protects mice from paraquat-induced lung injury: the important role of SIRT1 and NRF2 antioxidant pathways. Mol Med Rep 13:1833–1838
Lin HY, Tang HY, Davis FB, Davis PJ (2011) Resveratrol and apoptosis. Ann NY Acad Sci 1215: 79–88
Lin CJ, Lin HJ, Chen TH et al (2015) Polygonum cuspidatum and its active components inhibit replication of the influenza virus through toll-like receptor 9-induced interferon beta expression. PLoS One 10:1–13
Lin SC, Ho CT, Chuo WH et al (2017) Effective inhibition of MERS-CoV infection by resveratrol. BMC Infect Dis 17:1–10
Liu Y, Ma W, Zhang P et al (2015) Effect of resveratrol on blood pressure: a meta-analysis of randomized controlled trials. Clin Nutr 34:27–34
Liu Q, Zhu D, Jiang P et al (2019) Resveratrol synergizes with low doses of L-DOPA to improve MPTP-induced Parkinson disease in mice. Behav Brain Res 367:10–18
Lu X, Ji C, Xu H et al (2009) Resveratrol-loaded polymeric micelles protect cells from Abeta-induced oxidative stress. Int J Pharm 375:89–96
Lu X, Ma L, Ruan L et al (2010) Resveratrol differentially modulates inflammatory responses of microglia and astrocytes. J Neuroinflammation 8:1–14
Lu XY, Hu S, Jin Y et al (2012) Application of liposome encapsulation technique to improve anti-carcinoma effect of resveratrol. Drug Dev Ind Pharm 38:314–322
Lu DL, Ding DJ, Yan WJ et al (2013) Influence of glucuronidation and reduction modifications of resveratrol on its biological activities. Chembiochem 14:1094–1104
Luca SV, Macovei I, Bujor A et al (2020) Bioactivity of dietary polyphenols: the role of metabolites. Crit Rev Food Sci Nutr 60:626–659
Ma C, Wang Y, Dong L et al (2015) Anti-inflammatory effect of resveratrol through the suppression of NF-κB and JAK/STAT signaling pathways. Acta Biochim Biophys Sin Shanghai 47:207–213
Malaguarnera L (2019) Influence of resveratrol on the immune response. Nutrients 11:1–24
Malhotra A, Bath S, Elbarbry F (2015) An organ system approach to explore the antioxidative, anti-inflammatory, and cytoprotective actions of resveratrol. Oxidative Med Cell Longev 2015
Mancuso R, del Valle J, Modol L et al (2014) Resveratrol improves motoneuron function and extends survival in $SOD1^{G93A}$ ALS mice. Neurotherapeutics 11:419–432
Mastromarino P, Capobianco D, Cannata F et al (2015) Resveratrol inhibits rhinovirus replication and expression of inflammatory mediators in nasal epithelia. Antivir Res 123:15–21
Meng X, Zhou J, Zhao CN et al (2020) Health benefits and molecular mechanisms of resveratrol: a narrative review. Foods 9:1–27
Mihaylova MM, Shaw RJ (2011) The AMPK signalling pathway coordinates cell growth, autophagy and metabolism. Nat Cell Biol 13:1016–1023
Miki H, Uehara N, Kimura A et al (2012) Resveratrol induces apoptosis via ROS-triggered autophagy in human colon cancer cells. Int J Oncol 40:1020–1028
Moller M, Fjeldborg K, Juul M et al (2015) Resveratrol and inflammation: challenges in translating pre-clinical findings to improved patient outcomes. Biochim Biophys Acta Mol basis Dis 1852: 1124–1136
Mootha VK, Lindgren CM, Eriksson K-F et al (2003) PGC-1α-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. Nat Genet 34: 267–273
Moshawih S, Mydin RBSMN, Kalakotla S et al (2019) Potential application of resveratrol in nanocarriers against cancer: overview and future trends. J Drug Deliv Sci Technol 53:101187
Moussa C, Hebron M, Huang X et al (2017) Resveratrol regulates neuro-inflammation and induces adaptive immunity in Alzheimer's disease. J Neuroinflammation 14:1

Narayanan NK, Nargi D, Randolph C et al (2009) Liposome encapsulation of curcumin and resveratrol in combination reduces prostate cancer incidence in PTEN knockout mice. Int J Cancer 125:1–8
Neves AR, Lucio M, Martins S et al (2013) Novel resveratrol nanodelivery systems based on lipid nanoparticles to enhance its oral bioavailability. Int J Nanomedicine 8:177–187
Nicol T, Roc A, Mendoza-n M, Garc C (2020) The role of resveratrol on heavy metal-induced oxidative stress. Nutr Hosp 37:374–383
Nitulescu GM, Van De Venter M, Nitulescu G et al (2018) The Akt pathway in oncology therapy and beyond (review). Int J Oncol 53:2319–2331
Nunes S, Danesi F, Rio DD, Silva P (2018) Resveratrol and inflammatory bowel disease: the evidence so far. Nutr Res Rev 31:85–97
Olszowy M (2019) What is responsible for antioxidant properties of polyphenolic compounds from plants? Plant Physiol Biochem 144:135–143
Oroian M, Escriche I (2015) Antioxidants: characterization, natural sources, extraction and analysis. Food Res Int J 74:10–36
Palsamy P, Subramanian S (2010) Ameliorative potential of resveratrol on proinflammatory cytokines, hyperglycemia mediated oxidative stress, and pancreatic β-cell dysfunction in streptozotocin-nicotinamide-induced diabetic rats. J Cell Physiol 224:423–432
Pandita D, Kumar S, Poonia N (2014) Solid lipid nanoparticles enhance oral bioavailability of resveratrol, a natural polyphenol. Food Res Int 62:1165–1174
Patel KR, Scott E, Brown VA et al (2011) Clinical trials of resveratrol. Ann NY Acad Sci 1215: 161–169
Pecyna P, Wargula P, Murias M et al (2020) More than resveratrol: new insights into stilbene-based compounds. Biomol Ther 10(8):1111–1113
Penalva R, Esparza I, Larraneta E et al (2015) Zein-based nanoparticles improve the oral bioavailability of resveratrol and its anti-inflammatory effects in a mouse model of endotoxic shock. J Agric Food Chem 63:5603–5611
Penumathsa SV, Thirunavukkarasu M, Zhan L et al (2008) Resveratrol enhances GLUT-4 translocation to the caveolar lipid raft fractions through AMPK/Akt/eNOS signalling pathway in diabetic myocardium. J Cell Mol Med 12:2350–2361
Petrovski G, Gurusamy N, Das DK (2011) Resveratrol in cardiovascular health and disease. Ann NY Acad Sci 1215:22–33
Prysyazhna O, Wolhuter K, Switzer C et al (2019) Blood pressure-lowering by the antioxidant resveratrol is counterintuitively mediated by oxidation of cGMP-dependent protein kinase. Circulation 140:126–137
Ramos PS, Shedlock AM, Langefeld CD (2015) Genetics of autoimmune diseases: insights from population genetics. J Hum Genet 60:657–664
Raskovic A, Cucuz V, Torovic L et al (2019) Resveratrol supplementation improves metabolic control in rats with induced hyperlipidemia and type 2 diabetes. Saudi Pharmaceutical J 27: 1036–1043
Rayalam S, Yang J-Y, Ambati S et al (2008) Resveratrol induces apoptosis and inhibits adipogenesis in 3T3-L1 adipocytes. Phytother Res 22:1367–1371
Ruderman NB, Xu XJ, Nelson L et al (2010) AMPK and SIRT1: a long-standing partnership? Am J Physiol Endocrinol Metab 298:751–760
Saha A, Robertson E (2019) Mechanisms of B-cell oncogenesis induced by Epstein-Barr virus. J Virol 93:e002381–e0023813
Salehi B, Mishra A, Nigam M, Sener B, Kilic M, Sharifi-Rad M, Fokou P, Martins N, Sharifi-Rad J (2018) Resveratrol: a double-edged sword in health benefits. Biomedicines 6(3):91. https://doi.org/10.3390/biomedicines6030091
Samsamikor M, Daryani NE, Asl PR, Hekmatdoost A (2016) Resveratrol supplementation and oxidative/anti-oxidative status in patients with ulcerative colitis: a randomized, double-blind, placebo-controlled pilot study. Arch Med Res 47:304–309

Sanna V, Siddiqui IA, Sechi M et al (2013) Resveratrol-loaded nanoparticles based on poly(epsilon-caprolactone) and poly(D,L-lactic-co-glycolic acid)-poly(ethylene glycol) blend for prostate cancer treatment. Mol Pharm 10:3871–3881

Senturk S, Yaman M, Aydin H et al (2018) Effects of resveratrol on inflammation and apoptosis after experimental spinal cord injury. Turk Neurosurg 28(6):889–896

Seo Y, Park J, Choi W et al (2019) Antiatherogenic effect of resveratrol attributed to decreased expression of ICAM-1 (intercellular adhesion molecule-1). Arterioscler Thromb Vasc Biol 39: 675–684

Sessa M, Balestrieri ML, Ferrari G et al (2014) Bioavailability of encapsulated resveratrol into nanoemulsion-based delivery systems. Food Chem 147:42–50

Sharma AK, Keservani RK, Kesharwani RK (eds) (2018) Nanobiomaterials: applications in drug delivery. CRC Press. ISBN: 9781771885911

Shi Y, Zhou J, Jiang B, Miao M (2017) Resveratrol and inflammatory bowel disease. Ann N Y Acad Sci 1403:38–47

Shidhaye SS, Vaidya R, Sutar S et al (2008) Solid lipid nanoparticles and nanostructured lipid carriers—innovative generations of solid lipid carriers. Curr Drug Deliv 5:324–331

Shukla SD, Mahmood MQ, Weston S et al (2017) The main rhinovirus respiratory tract adhesion site (ICAM-1) is upregulated in smokers and patients with chronic airflow limitation (CAL). Respir Res 18:1–10

Silva F, Figueiras A, Gallardo E et al (2014) Strategies to improve the solubility and stability of stilbene antioxidants: a comparative study between cyclodextrins and bile acids. Food Chem 145:115–125

Singh UP, Singh NP, Busbee B et al (2012) Alternative medicines as emerging therapies for inflammatory bowel diseases. Int Rev Immunol 31:66–84

Singh DB, Gupta M, Kesharwani R, Sagar M, Dwivedi S, Misra K (2014) Molecular drug targets and therapies for Alzheimer's disease. Transl Neurosci 5(3):203–217

Soares MV, Puntel RL, Ávila DS (2018) Resveratrol attenuates iron-induced toxicity in a chronic post-treatment paradigm in *Caenorhabditis elegans*. Free Radic Res 52:939–951

Song J, Liu L, Hao K et al (2021) Resveratrol elongates the lifespan and improves antioxidant activity in the silkworm, *Bombyx mori*. J Pharmaceut Anal 11:374–382

Soo E, Thakur S, Qu Z et al (2016) Enhancing delivery and cytotoxicity of resveratrol through a dual nanoencapsulation approach. J Colloid Interface Sci 462:368–374

Springer M, Moco S (2019) Resveratrol and its human metabolites—effects on metabolic health and obesity. Nutrients 11:1–17

Sun Y, Reddy P (2013) Intracellular sensors of immunity and allogeneic hematopoietic stem cell transplantation. In: Immune biology of allogeneic hematopoietic stem cell transplantation, 2nd edn. Academic, San Diego, pp 425–447

Sun L, Chen B, Jiang R et al (2017) Resveratrol inhibits lung cancer growth by suppressing M2-like polarization of tumor associated macrophages. Cell Immunol 311:86–93

Szkudelsk K, Okulicz M, Hertig I et al (2020) Resveratrol ameliorates inflammatory and oxidative stress in type 2 diabetic Goto-Kakizaki rats. Biomed Pharmacother 125:110026

Szkudelska K, Szkudelski T (2010) Resveratrol, obesity and diabetes. Eur J Pharmacol 635:1–8

Szkudelski T, Szkudelska K (2011) Anti-diabetic effects of resveratrol. Ann N Y Acad Sci 1215: 34–39

Takashina M, Inoue S, Tomihara K et al (2017) Different effect of resveratrol to induction of apoptosis depending on the type of human cancer cells. Int J Oncol 50:787–797

Taniguchi K, Karin M (2018) NF-B, inflammation, immunity and cancer: coming of age. Nat Rev Immunol 18:309–324

Teijaro JR (2016) Type I interferons in viral control and immune regulation. Curr Opin Virol 16:31–40

Tellone E, Galtieri A, Russo A et al (2014) Resveratrol: a focus on several neurodegenerative diseases. Oxidative Med Cell Longev 2015:392169

Thapa SB, Pandey RP, Il Park Y, Sohng JK (2019) Biotechnological advances in resveratrol production and its chemical diversity. Molecules 24:1–21
Timmers S, Konings E, Bilet L et al (2011) Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. Cell Metab 14: 612–622
Tome-Carneiro J, Larrosa M, Gonzalez-Sarrias A et al (2013) Resveratrol and clinical trials: the crossroad from in vitro studies to human evidence. Am J Phys Med Rehabil 19:6064–6093
Torres J, Mehandru S, Colombel J-F, Peyrin-Biroulet L (2017) Crohn's disease. Lancet 389:1741–1755
Tsai M-H, Hsu L-F, Lee C-W et al (2017) Resveratrol inhibits urban particulate matter-induced COX-2/PGE2 release in human fibroblast-like synoviocytes via the inhibition of activation of NADPH oxidase/ROS/NF-κB. Int J Biochem Cell Biol 88:113–123
Vélez-Marín M, Souza LFU-V, Lenz MI (2012) Papel Del Resveratrol De Uva Como Antioxidante. Luna Azul 34:240–256
Venuti V, Cannava C, Cristiano MC et al (2014) A characterization study of resveratrol/sulfobutyl ether-beta-cyclodextrin inclusion complex and *in vitro* anticancer activity. Colloids Surf B: Biointerfaces 115:22–28
Walle T, Hsieh F, DeLegge MH et al (2004) High absorption but very low bioavailability of oral resveratrol in humans. Drug Metab Dispos 32:1377–1382
Wang P, Sang S (2018) Metabolism and pharmacokinetics of resveratrol and pterostilbene. Biofactors 44:16–25
Wang XX, Li YB, Yao HJ et al (2011) The use of mitochondrial targeting resveratrol liposomes modified with a dequalinium polyethylene glycol-distearoylphosphatidyl ethanolamine conjugate to induce apoptosis in resistant lung cancer cells. Biomaterials 32:5673–5687
Wang B, Sun J, Li X et al (2013) Resveratrol prevents suppression of regulatory T-cell production, oxidative stress, and inflammation of mice prone or resistant to high-fat diet–induced obesity. Nutr Res 33(11):971–981
Wang Z, Zhang J, Duan Y et al (2015) MicroRNA-214 participates in the neuroprotective effect of resveratrol via inhibiting α-synuclein expression in MPTP-induced Parkinson's disease mouse. Biomed Pharmacother 74:252–256
Wang G, Hu Z, Song X et al (2017a) Analgesic and anti-inflammatory activities of resveratrol through classic models in mice and rats. Evid Based Complement Alternat Med 2017:5197567
Wang X, Li T, Li J et al (2017b) The effects of resveratrol on inflammation and oxidative stress in a rat model of chronic obstructive pulmonary disease. Molecules 22(9):1529
Wark PAB, Johnston SL, Moric I et al (2002) Neutrophil degranulation and cell lysis is associated with clinical severity in virus-induced asthma. Eur Respir J 19:68–75
Wenzel E, Somoza V (2005) Metabolism and bioavailability of trans-resveratrol. Mol Nutr Food Res 49:472–481
WHO World Health Organization (2020a) Obesity and overweight. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed 28 Sept 2020
WHO World Health Organization (2020b) Diabetes. https://www.who.int/es/news-room/fact-sheets/detail/diabetes. Accessed 28 Sept 2020
Wiciński M, Malinowski B, Rajewski P et al (2020) Resveratrol's impact on vascular smooth muscle cells hyporeactivity: the role of rho-kinase inhibition. Biomed Res Int 9012071
Xie XH, Zang N, Min LS et al (2012) Resveratrol inhibits respiratory syncytial virus-induced IL-6 production, decreases viral replication, and downregulates TRIF expression in airway epithelial cells. Inflammation 35:1392–1401
Xing L, Casasnovas JM, Cheng RH (2003) Structural analysis of human rhinovirus complexed with ICAM-1 reveals the dynamics of receptor-mediated virus uncoating. J Virol 77:6101–6107
Yamamoto Y, Gaynor RB (2001) Therapeutic potential of inhibition of the NF-κB pathway in the treatment of inflammation and cancer. J Clin Investig 107:135–142
Yan B, Cheng L, Jiang Z et al (2018) Resveratrol inhibits ROS-promoted activation and glycolysis of pancreatic stellate cells via suppression of miR-21. Oxidative Med Cell Longev 2018:1–15

Yanez M, Jhanji M, Murphy K et al (2019) Nicotinamide augments the anti-inflammatory properties of resveratrol through PARP1 activation. Sci Rep 9:1–10
Yang X, Jiang T, Wang Y et al (2019) The role and mechanism of SIRT1 in resveratrol-regulated osteoblast autophagy in osteoporosis rats. Sci Rep 9:1–15
Yoon H, Dehart JP, Murphy JM, Lim STS (2015) Understanding the roles of FAK in cancer: inhibitors, genetic models, and new insights. J Histochem Cytochem 63:114–128
Yun CW, Lee SH (2018) The roles of autophagy in cancer. Int J Mol Sci 19:1–18
Zhang XS, Li W, Wu Q et al (2016) Resveratrol attenuates acute inflammatory injury in experimental subarachnoid hemorrhage in rats via inhibition of TLR4 pathway. Int J Mol Sci 17:1–14
Zhang L, Yu X, Ji M et al (2018) Resveratrol alleviates motor and cognitive deficits and neuropathology in the A53T α-synuclein mouse model of Parkinson's disease. Food Funct 9:6414–6426
Zhou Z, Mou S, Chen X et al (2018) Anti-inflammatory activity of resveratrol prevents inflammation by inhibiting NF-κB in animal models of acute pharyngitis. Mol Med Rep 17:1269–1274
Zhou X, Yang J, Zhou M et al (2019) Resveratrol attenuates endothelial oxidative injury by inducing autophagy via the activation of transcription factor EB. Nutr Metab 16:1–12