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Grape Secondary Metabolites – Benefits for Human Health

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1. Introduction

Grapevine is one of the ancient crops linked with human history during the evolutionary development of man. The fruits and wine have taken part in daily life and ancient ceremonies of our predecessors and currently grapevine is one of the most widely cultivated fruit crop in the world. It is consumed fresh, dry or as beverage but the most popular consumption form in the world is wine. Recent decades researchers found another reason to praise grape products: its beneficial effect on health. In the late Eighties grape and wine have been in the spotlight because of the finding of so called 'French Paradox' that linked moderate red wine consumption to a lower incidence of cardiovascular disease. As an addition, epidemiological studies demonstrated the beneficial effect of moderate wine intake on the neurodegenerative process (Marambaud et al., 2005). These findings gave boost to numerous studies of grape and wine effects on health, revealing evidences about the protective effect of grape compounds against cancer and age-related disorders, such as certain neurological diseases and metabolic disorders. Moreover, scientists proved that some compounds of grape are implicated in important biological functions in the body such as antioxidant defense system, immunological regulation and anti-inflammatory processes. The main question is what makes grape so useful and healthy?

The answer is found in the fruit and wine constituents, i.e. grape secondary metabolites. The secondary metabolites are exclusively produced by plants and represent more than 30 000 different substances that give individual properties of plant species and define them as healthy, healing or even poisonous. Grape is rich in secondary metabolites which makes this fruit crop so popular among the scientific society. Different research groups have undertaken the study of grape metabolomics and revealed the rich profile of grape and wine, including polyphenols such as resveratrol, caffeic acid, catechin, quercetin etc., all of which present highly bioactive substances. In recent years the analyses of grape composition and its effect on human health led to the conclusion that resveratrol is one of the key grape substances responsible for the preventive and therapeutic abilities of wine. Recent study of Iriti et al. (2006) discovered another key substance in grape - melatonin, which is considered for one of the most powerful antioxidants involved in various physiological functions in human body (Srinivasan et al., 2006). It is noteworthy that the health promoting effects of grape and wine are due to the secondary metabolites presented in them.

2. Resveratrol

Resveratrol is one of the polyphenol substances which are considered to have antioxidant activities and to extend life (Lagouge et al., 2006). Resveratrol is a stilbene which is produced naturally by more than 70 plant species as a defensive reaction against pathogens or under stress conditions (UV radiation). As far as resveratrol is a phytoalexin it is produced in plants during the process of a long-term resistance to a certain pathogens or abiotic stress and it is reported that in grapes resveratrol provides a resistance to fungal diseases (LeBlanc, 2006). Resveratrol is soluble in fats and exists in two isomeric forms: cis and trans. Both forms could be bound to a glucose molecule so that resveratrol also occurs naturally as glucoside in grapes which is known as piceid.

Resveratrol is naturally occurring in grapevines where it is almost exclusively synthesized in berry skins, but in muscadine grapes it is found also in seeds (LeBlanc, 2006). The content of this substance in red grapes is higher than in white ones. Total resveratrol content in 100 g red grapes varies between 0.15 mg and 0.78 mg. It is estimated that fresh grape skins contain between 50 and 100 µg resveratrol per gram wet weight (Baliga et al., 2005). The levels of resveratrol in grape are influenced by grape cultivar, its geographic origin and exposure to a fungal disease or other stress conditions. It is found that during the process of winemaking this substance could increase its content depending on fermentation time during which the wine spends in contact with the grape skins. Therefore, the content of resveratrol in white wines is considerably lower since this wine is made after removing the grape skins. In contrary red wine is fermented with the grape skins allowing the wine to absorb more quantity of resveratrol. Some reports suggest that during the winemaking process resveratrol glucosides (piceids) convert to resveratrol and thus the higher concentration of the substance in wine in comparison of that found in fresh grape juice is explained (LeBlanc, 2006).

Recently, scientists are interested in biological activity of phytoalexins and their effect on human health. According to data concerning incidences of coronary heart disease collected from World Health Organization (WHO) in the period of 80s-90s last century, it is reported that French people suffer less from this disease despite having a diet relatively rich in saturated fats and this fact is known as a French paradox (LeBlanc, 2006). Different research groups were investigating the reason for French paradox and why French people have less incidences of coronary heart disease in comparison with Americans although the fact that French consume daily in average more saturated fats (15,6% of total energy intake) than American people (11,3% of total energy intake) (Elmadfa & Kornsteiner, 2009). It has been suggested that the high consumption of red wine in France is a primary factor for the French paradox. The data suggest that wine consumption reduces coronary heart diseases much more than other alcohol beverages and therefore the presence of other wine components different from alcohol provide higher prevention of heart diseases. An increased interest in wine bioactive compounds gave a boost in research of resveratrol and its effect on human health.

2.1 Resveratrol and its cardioprotective effect

The occurrence of the French paradox boosted the researchers to analyze the effect of resveratrol on people with a known predisposition to cardiovascular heart disease. A recent study of Sacanella et al. (2007) reported that 2 glasses of 100 ml red wine per day for 4 weeks is resulting in a greater reduction of inflammatory biomarkers, cellular adhesion molecules

and monocyte adhesion to endothelium, which is not found for the white wine. Resveratrol is a key constituent of red wine which has variety of activities associated with its cardioprotective effect. This assertion is well-founded with the results from Hung's research showing that synthesized and purified trans-resveratrol is effective to prevent reperfusion-induced arrhythmias and mortality in rats (Hung et al., 2000). It is considered that the protective mechanism of resveratrol is due to its activity as intracellular antioxidant, anti-inflammatory agent, and due to its ability to induce angiogenesis and expression of nitric oxide synthase (Bhat et al., 2001) as well to block low-density lipoprotein (LDL) peroxidation and increase the levels of high-density lipoprotein (HDL) (Petrovski et al., 2011). In the study conducted by Klinge et al. (2008) are analyzed the signaling pathways and molecular mechanisms by which resveratrol in concentrations compatible with oral consumption (nanomolar concentrations) is activating the protection against coronary heart diseases and is improving the function of endothelium of blood vessels. It is found that nanomolar concentration of this compound is enough to stimulate rapidly nitric oxide production in endothelial cells by increasing the interaction between estrogen receptor α -Src and calveolin-1, which is one of the components of signaling pathway of resveratrol's protective action. As far as inflammation plays a key role in atherosclerosis, resveratrol can attenuate the condition through its anti-inflammatory effect, which involves inhibition of the synthesis of pro-inflammatory compounds such as prostaglandin E₂ and interleukin-6 (Petrovski et al., 2011). Another cardioprotective mechanism of resveratrol is its ability to inhibit platelet aggregation, thus preventing formation of thrombi (Petrovski et al., 2011).

Another important side of resveratrol's heart protective effect is its participation in so called 'preconditioning' which is known to be one of the most powerful technique for promoting a cardioprotection (Das et al., 1993; Sato et al., 2000). The preconditioning includes several short cycles of reversible ischemia, each followed by another short duration of reperfusion. The process of preconditioning-mediated cardioprotection makes the heart resistant to subsequent lethal ischemic injury (Das & Maulik, 2006). Preconditioning induces the expression of some heat shock proteins and endogenous antioxidant enzymes such as superoxide dismutase and also enhances the signal transduction by activating the survival signals and inhibiting the death ones. Recent study of Das & Maulik (2006) reported that resveratrol may act as a phytopharmacological preconditioning agent by activation of signaling pathways of preconditioning. These pathways include activation of adenosine A₁ and A₃ receptors, multiple kinases, K_{ATP} mitochondrial ATP-sensitive potassium channel and nitric oxide production - all of them are important factors with crucial role in preconditioning-mediated cardioprotection (Das & Maulik, 2006; Petrovski et al., 2011). Resveratrol provides cardioprotection by improving postischemic recovery and reducing the size of myocardial infarct and cardiomyocyte apoptosis (Das & Maulik, 2006). However, the mechanisms of enhancing the heart endogenous defense are not completely clear and more studies are necessary for better understanding of these signaling pathways.

2.2 Resveratrol and its therapeutic potential in neurological disorders

In addition to the cardioprotective effect of resveratrol, recent data suggest that this phytoalexine has protective and therapeutic potential against certain neurological disorders. Neurodegenerative diseases are one of the significant challenges of medicine and involve malfunction or progressive loss of structure of neurons and even cell death. Although the profound research in this area, so far the mechanisms of diseases pathologies are poorly understood. Many of these diseases are heritable and caused by genetic mutations. Other

causes of such disorders include toxins, chemicals and certain medical conditions such as alcoholism or stroke. With the research progress it has been hypothesized that the oxidative stress and damage caused by reactive oxygen species (ROS) play a major role in neurodegeneration (Pallàs et al., 2009). The oxidative stress is induced by imbalance between production and detoxification of ROS leading to damage of all cell components, including DNA, proteins, lipids and even neuronal messengers. This could lead to irreversible damage of neuron structure and function, thus contributing to the pathogenesis of neurodegeneration. Other toxic reactions that cause neurodegeneration involve inflammation and dysfunction of mitochondrial activity (Ramassamy, 2006). As far as resveratrol is reported to have a strong antioxidant and anti-inflammatory activity its beneficial properties could be used in the treatment and prevention of neurodegenerative diseases. Epidemiological studies have shown that the moderate red wine consumption is correlated with a significant reduction of Alzheimer's disease and dementia (Marambaud et al., 2005; Orgogozo et al., 1997). Furthermore, *in vivo* studies with animals demonstrate the protective effect of resveratrol in models of neurotoxicity (Virgili & Contestabile, 2000). These results gave boost of studying the molecular targets of resveratrol as a potential phytochemical in neurological diseases. The most common neurodegenerative disorders include Alzheimer's, Parkinson's and Huntington's diseases.

2.2.1 Alzheimer's disease (AD)

AD is the most common form of dementia, which is associated with senile plaques caused by aggregation of β -amyloid peptide (β AP). It has been shown that intra- and extra-cellular β AP is responsible for the initiation of synaptic malfunctions and occurrence of AD-symptoms (Wirths et al., 2004). Yu and colleagues (2006) reported that β APs can cause massive neuronal cell loss by inducing apoptosis. It is suggested that β APs trigger the apoptosis by interaction with various neuronal receptors and free radical production that activate different cell-death-signalling pathways (Yuan & Yankner, 2000). Valerio et al. (2006) found that the activation of protein complex NF- κ B in microglia plays a crucial role in β AP-induced neuronal cell death. This signaling pathway can be modulated and significantly reduced by inhibition of the degradation of cytoplasmatic protein I κ B that acts as an inhibitor of NF- κ B. That very pathway is reported to be a target of resveratrol, where the grape compound inhibits the degradation of I κ B thus showing neuroprotective and therapeutic effect (Pallàs et al., 2009).

In a study Marambaud et al. (2005) investigated whether resveratrol is modulating the levels of β APs in the neocortex and hippocampus of brains damaged from AD. The *in vitro* research reports that the β AP levels were significantly decreased in cells treated with resveratrol. Further *in vitro* experiments demonstrate that the polyphenol promotes intracellular degradation of β APs without increasing the total protease activity (Marambaud et al., 2005).

Another possible therapeutic mechanism of resveratrol is its similarity with the effects of calorie restriction. In the survey of Pallàs et al. (2009) are discussed studies, which demonstrated that short-term calorie restriction is associated with reduction of β AP-plaques in transgenic mouse models of AD. It is suggested that the dietary regime promotes processing of the amyloid precursor protein via pathway that does not result in β APs. This is possible when the processing is made by α -secretase cleavage instead of β - and γ -secretases. As far as resveratrol mimics the calorie restriction pathways, it can be hypothesized that it reduces the β APs using the same pathway (Pallàs et al., 2009).

Moreover, β APs induce apoptosis via production of reactive oxygen species, which can be scavenged by the strong anti-oxidation effect of resveratrol (Jang et al., 2007). These data prove that resveratrol stimulates the clearance of senile plaques and prevents from the neurotoxic effect of β APs, thus having a neuroprotective effect.

Inflammation, being associated with the development of AD, is another target of resveratrol. The anti-inflammatory properties of resveratrol have a beneficial effect on prevention and treatment of neurodegenerative process.

2.2.2 Parkinson's disease (PD)

PD is another neurodegenerative disorder that is characterized by a selective death of dopamine-producing cells in the substantia nigra (Gao et al., 2002). As contributing factors to the disease, mitochondrial dysfunction, inflammation, oxidative stress and apoptosis appear to have a major role in the development and progression of PD. Recent studies showed that resveratrol has neuroprotective function against the deleterious effect of 6-hydroxydopamine (6-OHDA) in rat models of PD (Jin et al., 2008; Khan et al., 2010). The conducted trials revealed that resveratrol suppresses the expression of pro-inflammatory cytokines (TNF- α) and enzymes (COX-2), which play a key role in the inflammatory process that is related with the progression of neurodegenerative diseases. Jin et al. (2008) demonstrated that the overexpression of COX-2 and TNF- α mRNA is involved in the pathogenesis of PD and resveratrol can be used to reduce the levels of these proteins, resulting in improvement of pathological lesions in substantia nigra neurons in rat models of PD. These results confirm the beneficial effect of resveratrol in the treatment of PD.

2.2.3 Huntington's disease (HD)

HD is a neurodegenerative genetic disorder caused by a mutation of the gene coding Huntingtin protein. The mutation results in synthesis of a different form of the protein that forms aggregates with neurotoxic effect leading to degeneration of specific brain areas. The mutant protein damages mitochondria in the affected neurons, causing dysfunction and death of the cells. One of the experimental models of HD is the utilization of the neurotoxin 3-nitropropionic acid on rodents. One of the major mechanisms of toxin action is the induction of mitochondrial dysfunction via oxidative stress. Several studies reported the protection activity of resveratrol against this neurotoxin and suggested that it was its antioxidant properties that are responsible for the prevention of the functional effect of the toxin (Binienda et al., 2010; Kumar et al., 2006). Furthermore, some authors reported that the beneficial effect of resveratrol is through activation of SIRT1 (Howitz et al., 2003; Lagouge et al., 2006). However, Pallos et al. (2008), working with *Drosophila* model of HD, demonstrated that resveratrol has a neuroprotective effect in a dose-dependent manner but through mechanisms that are independent of Sir2 activation (the human ortholog is SIRT1). Another research demonstrates that the phenolic constituents of red wine can inhibit the harmful effect of oxidative stress as a result of nitric oxide production (Bastianetto et al., 2000), which is neurodegenerative event with damages relevant to those occurring during chronic inflammation, cerebral ischemia or excitotoxicity. The *in vitro* study showed that resveratrol is capable of protecting and rescuing rat's hypothalamic cells against nitric oxide - induced toxicity (Bastianetto et al., 2000).

Hence, the results from the above mentioned studies lead to the conclusion that the red wine polyphenol constitute, resveratrol, possesses a therapeutic potential and has a beneficial effect for the prevention of age-related neurodegenerative disorders. The data

about the antioxidant activities of resveratrol support the hypothesis of beneficial effects of moderate daily red wine consumption against the occurrence of neuropathological diseases of chronic or acute nature. Presented studies confirm the neuroprotective value of resveratrol and its ability to rescue neuron cells but yet the exact mechanisms and pathways of its action remain not fully revealed and further studies are needed.

2.3 Resveratrol and its longevity and anti-ageing properties

Ageing processes are determined by metabolic disorders which occur with the age increasing. Metabolic disorders are tightly linked to compromised mitochondrial functions (Petersen et al., 2003) as a result of reduced expression of genes controlling mitochondrial biogenesis in humans and animals (Lagouge et al., 2006). Numerous studies revealed that the gene PGC-1 α (peroxisome proliferator-activated receptor γ co-activator) has a crucial role in mitochondrial activity (Wu et al., 1999), skeletal muscle fiber-type switching (Puigserver & Spiegelman, 2003), controlling of adaptive thermogenesis (Puigserver et al., 1998) and together with SIRT1 gene promotes the adaptation to caloric restriction (Rodgers et al., 2005). SIRT1 gene encodes a member of sirtuin family of proteins and interacts with PGC-1 α , taking part in regulation of longevity, apoptosis and DNA repair (Sinclair, 2005). Recent studies showed that resveratrol significantly increases the SIRT1 activity through allosteric interaction (Howitz et al., 2003). In the *in vivo* animal studies conducted by Lagouge et al. (2006) is demonstrated that resveratrol impacts on the regulation of energy homeostasis by inducing mitochondrial activity through increasing SIRT1 activity and thus modulating PGC-1 α functions. In series of experiments is demonstrated that the intake of resveratrol 200 or 400 mg/kg/day has a beneficial effect on body weight by inducing a resistance to weight gain and enhances the adaptive thermogenesis by increasing the cold tolerance (Lagouge et al., 2006). Resveratrol treatment induces mitochondrial morphological changes in muscles and brown adipose tissue such as enlarging of mitochondrial structures and increasing presence of cristae and thus the polyphenol has a beneficial influence on the energy homeostasis and reduces the weight gaining in conditions of high fat diet.

As far as resveratrol changes the morphological structure of mitochondria in muscles, this substance enhances the enzymatic activity of organelles and induces the muscle fiber-type switching resulting in increased resistance to muscle fatigue (Booth et al., 2002). All these data lead to the conclusion that resveratrol enhances mitochondrial activity resulting in suppression of ageing symptoms by increasing of fatty acid oxidation, amelioration of fat burning, maintaining of energy homeostasis and induction of muscle fatigue resistance.

Besides its anti-ageing properties, there are evidences that resveratrol works as a longevity agent. In year 2003 the team of David Sinclair reported that resveratrol increases cell survival by stimulating SIRT1-dependent deacetylation of p53 tumor suppressor (Howitz et al., 2003). Nevertheless, some studies with yeast (Kaeberlein et al., 2004) and nematode *Caenorhabditis elegans* (Guarente & Picard, 2005) questioned the involvement of sirtuin in lifespan extension leaving this assertion quite controversial (Markus & Morris, 2008). These results suggest that the wide effects of resveratrol are not always a result of sirtuin activation. In the recent review of Markus & Morris (2008) is revealed that resveratrol is also involved in sirtuin-independent pathway which is central to the control of lifespan. In this pathway the target of resveratrol is PI3K (phosphoinositide 3-kinase) which implicates the polyphenol in insulin-like signaling pathway for activating of mitochondrial biogenesis (Frojdo et al., 2007).

The reports that resveratrol has positive effect on lifespan extension in mice prompt to more extensive research of *in vivo* resveratrol's effects in mammals (Baur et al., 2006; Lagouge et al., 2006). The findings of the French (Lagouge et al., 2006) and American (Baur et al., 2006) research groups are promising for therapeutic properties of resveratrol in human metabolic disorders.

3. Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is an indoleamine, a naturally occurring compound found in animals, plants and microbes. In human body melatonin plays an important role for regulation of sleep-wake cycles, induction of immune system, sexual development and vascular tone (Iriti et al., 2006).

For a long time it was thought that melatonin is a neurohormone exclusively synthesized in vertebrates, but in recent years it was found that this substance is presented in plants, bacteria, algae, fungi and invertebrates (Iriti & Faoro 2006). Few years ago, Iriti et al. (2006) discovered melatonin in different grape cultivars, which gave a boost of series of studies concerning the presence and biosynthesis of this compound in grape and wine (Guerrero et al., 2008; Mercolini et al., 2008). Melatonin content in grape is reported to range from 5 to 96 pg/g, while in wine the content was found to vary from 50-80 pg/ml (Spanish wines) to 400-500 pg/ml (Italian wines) with higher content in red wines (Iriti et al., 2010). It was reported that the human serum concentration of melatonin significantly increases 1 hour after intake of 100 ml red wine (Guerrero et al., 2008), resulting in increased plasma antioxidant capacity. These results show that the effect of this neurohormone in humans could be modulated by moderate administration of wine. Recent studies are directed to melatonin treatment of cancer, immune disorders, cardiovascular diseases, depression, circadian rhythm sleep disorders and sexual dysfunction. Therefore, the reported presence of melatonin in grape and wine gives an additional support to the hypothesis about the beneficial health effects of moderate wine consumption.

3.1 Antioxidant properties of melatonin

Melatonin is a pervasive substance whose powerful antioxidant property is particularly directed to a protection of nuclear and mitochondrial DNA by scavenging OH, O₂⁻, H₂O₂, NO and inhibition of lipid peroxidation. Reiter et al. (2003) reported melatonin to be an efficient scavenger of free radicals in mitochondria, which are a major source of reactive species in the cell. Moreover, the authors reported that melatonin suppresses the apoptotic signals originating in mitochondria, thus diminishing disorders that are related to mitochondrial dysfunction – brain damages, age-related disease, etc. It was found that melatonin is effective against brain damages caused by release of free radicals containing oxygen atom (Tütüncüler et al., 2005) and also can reduce the brain damages caused by some types of Parkinson's disease. The antioxidant effect of melatonin provides a protection from neurodegeneration as well as from the mutagenic and carcinogenic actions of free radicals and thus, melatonin contributes enhancing of longevity (Oaknin-Bendahan et al., 1995).

Other evidence concerning the strong antioxidative properties of melatonin is its positive effect for successful treatment for septic shock in newborns, which is discussed by Reiter et al. (2003). As far as the excessive free radical generation is considered to be one of the causes for sepsis the authors attributed the beneficial actions of melatonin to its antioxidant properties. Moreover, in this review the authors presented numerous evidences about the

positive effect of melatonin in treatment of a variety of conditions associated with elevated oxidative stress in newborns, children and adults (Reiter et al., 2003).

So far, the obtained information from numerous studies, some of which are above mentioned, leads to the conclusion that melatonin acts on multiple ways for reduction of oxidative stress, i.e. direct scavenge of free radicals and reactive species, stimulation of antioxidative enzymes, stimulation of mitochondrial function, synergy with classic antioxidants, etc. The powerful direct and indirect antioxidant actions of melatonin, proved by *in vitro* and clinical tests, are promising for prevention and treatment of disease states that involve damage caused by free radicals.

3.2 Melatonin effects on nervous system

As far as melatonin in mammals plays a role of neurohormone, it is obviously that it is involved in various function associated with nervous system. It has a key role in regulation of circadian rhythm that coordinates sleep-wake cycle and takes part in modulation of mood and behavior. Since melatonin (exogenous and endogenous) possesses the ability to pass the blood-brain barrier it has a direct effect on brain. Moreover, it is reported that melatonin from edible plants binds to melatonin receptors in mammalian brain and exerts its biological activity (Iriti et al., 2010). Melatonin has a broad range of action, which is not limited only to the regulation of circadian rhythm. Findings from mice and rat trials have shown that melatonin receptors appear to play important role in mechanisms of learning and memory (Larson et al., 2006) as well as that melatonin facilitates short-term memory (Argyriou et al., 1998). The study conducted by Baydas and co-workers (2002) suggested that the beneficial effect of melatonin on memory and learning processes could be due to its involvement in structural remodeling of synaptic connections during these processes. In another study is demonstrated the powerful antioxidant effect of melatonin in ethanol-treated rats where melatonin prevents lipid peroxidation in brain resulting from chronic ethanol exposure (Gönenç et al., 2005).

The melatonin acts through three main mechanisms, namely receptor-mediated, protein-mediated and non-receptor-mediated. The receptor-mediated activity of melatonin involves membrane (MT_1 and MT_2) and nuclear receptors ($ROR\alpha$ and $RZR\beta$) and is responsible for the immune system and upregulation of antioxidant enzymes (Srinivasan et al., 2006). The non-receptor-mediated action of melatonin involves its antioxidant properties as a direct scavenger of reactive species.

Interestingly, melatonin secretion decreases with ageing, which was suggested to be associated with the manifestation of age-related neurodegenerative diseases (Srinivasan et al., 2006). Moreover, it is reported a significant reduction of melatonin secretion in people with dementia in comparison with nondemented controls (Papolla et al., 1997), thus, suggesting exogenous melatonin to be extensively explored as a therapeutic and preventive agent in neurodegenerative diseases.

3.2.1 Alzheimer's disease (AD)

It has been reported by many researchers that the melatonin levels are much lower in AD patients in comparison with the hormone levels detected in aged matched controls (Skene & Swaab, 2003). Another finding indicated one of the melatonin receptors (MT_2) to mediate the melatonin effects in human hippocampus – a mechanism that appear to be impaired in AD patients (Savaskan et al., 2005). The study of Savaskan et al. (2005) is the first immunohistochemical assay that identifies the exact cellular distribution of MT_2 in human

hippocampus and proves the altered expression and cellular loss of this receptor in AD patients. All these data prove the importance of melatonin and its targets for the neurological processes and suggest its beneficial effect for treatment of AD.

As far as deposition of cerebral β APs is a primary hallmark of AD, the effect of melatonin against the neurotoxic properties of β APs is examined. It was found that melatonin prevents death of cultured neuronal cells caused by exposure to β APs (Pappolla et al., 1997). As an addition, the oxidative stress, along with the neurotoxicity of β APs, is proposed to play a significant role in the pathogenesis of AD lesions. Pappolla et al. (1992) first presented evidences that proof the role of oxidative damage in the development and progression of AD. These finding was confirmed by recent trial with transgenic mouse models of AD (Feng et al., 2006). Both, oxidative stress and deposition of β APs, were found to be related with damage and severe modifications of brain lipids, proteins and DNA and to trigger apoptosis in AD brain (Feng et al., 2006). The authors summarize that these neuronal alterations in certain regions of AD brains are indicated by some pro-apoptotic markers such as increased levels of Par-4 (proapoptotic protein), elevated expression of Bax (apoptosis-effector gene) and upregulated caspases (enzymes, main executors of apoptosis). In this study the authors demonstrated that in transgenic mouse models of AD the early melatonin supplement prevents the abnormal upregulation of pro-apoptotic markers, thus inhibiting the consequential initiation of apoptotic cascade (Feng et al., 2006). However, melatonin fails in reducing β APs-plaques and expressing antioxidant activity in old transgenic mouse models with already established AD (Quinn et al., 2005), thus limiting the therapeutic properties of exogenous melatonin only to the early stages of the disease. Nevertheless, the demonstrated neuroprotective effect of melatonin supplement in the early stage of AD (Feng et al., 2006) is promising for the prevention of AD development. Even though melatonin cannot inhibit the AD progression when it is in advanced stage, it shows to be useful in symptomatic treatment concerning sleep disturbance, sundowning etc. (Srinivasan et al., 2006).

3.2.2 Parkinson's disease (PD) and Huntington's disease (HD)

Several studies demonstrated the neuroprotective effect of melatonin in experimental models of PD. The protective effect is suggested to be complex due to the multiple targets involved in the melatonin action against oxidative stress, which is reviewed by Srinivasan (2002) and Srinivasan et al. (2005). However, some studies, summarized in the profound review of Srinivasan et al. (2006), reported about adverse effect of melatonin leading to aggravation of motor deficit in animal models of PD. The presence of such contradictory results concerning melatonin action in PD models calls for more profound studies in this area.

A large body of evidence supports the thesis that mitochondrial dysfunction and defects in brain energy metabolism trigger HD. Thus, the oxidative stress, excitotoxicity and apoptosis play crucial role in the pathogenesis of HD. Therefore, the powerful anti-oxidant property of melatonin is proposed to have beneficial effect in HD patients. The experimental animal models of the disease use neurotoxins, quinolinic acid or 3-nitropropionic acid, to mimic mitochondrial dysfunction. When the effect of melatonin is tested in both models, the results showed prevention of oxidative stress damage and cell death in the quinolinic acid-model (Southgate et al., 1998) and protection of brain structures after induced oxidative stress in 3-nitropropionic acid-models (Túnez et al., 2004). These results confirm the neuroprotective ability of melatonin against induced oxidative stress, but more experiments are needed to elucidate the melatonin effect on the other key factors of the disease - excitotoxicity and apoptosis.

Although various experimental models of AD, PD and HD prove the ability of exogenous melatonin to counteract diseases progression, the exact direct and indirect pleiotropic mechanisms of hormone actions are not completely revealed. Since central nervous system is highly susceptible to oxidative stress, it is suggested that the beneficial effect of melatonin is mostly due to its powerful antioxidant activity exerted at various levels. However, the research work in this area should be continued in order to elucidate the therapeutic potential of exogenous melatonin in neurodegenerative disorders.

All these data suggest that melatonin is an important substance associated with numerous health benefits. Recent results proved that melatonin presented in plant foods preserves its bioavailability and suggest that it may counteract numerous disease conditions, including age-related and neurological disorders, carcinogenesis, cardiovascular diseases and diabetes (Iriti et al., 2010). It is noteworthy that grape and wine appear to be a rich source of melatonin and interestingly, it is found that melatonin level in grape could be increased by agrochemical treatments, while its level in wine may be modulated during the indoleamine synthesis by yeasts during the fermentation process of winemaking (Iriti et al., 2006). The presence of melatonin in these products gives new evidence for the healthpromoting effect of grape and wine.

Grape and wine are rich in phytochemicals but it is still little known about their beneficial effects on human health. Thus, metabolomics offers an opportunity for revealing the properties of a large number of plant secondary metabolites and for better understanding of their phytochemical effects on humans.

4. Conclusions

So far, metabolite analyses of grape showed its rich content of secondary metabolites, which are highly beneficial for human health. This brief presenting of evidences about the beneficial effects of resveratrol and melatonin reveal only a little part of the effectiveness of grape secondary metabolites. The above reported data about very few grape secondary metabolites (resveratrol and melatonin) proved their biological potential as natural antioxidants, therapeutic agents for numerous pathological disorders and demonstrated the significance of grape and wine compounds. These natural substances showed an enormous promise for utilization as phytochemicals for prevention and treatment of diseases (cancer, cardiovascular diseases, neurodegenerative disorders and others) which are so common for our society. However, it is still not completely clear which of the cellular mechanisms and signaling pathways are involved or activated by these phytochemicals in the processes of disease prevention and therefore more detailed research in this area is necessary.

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Advanced Understanding of Neurodegenerative Diseases focuses on different types of diseases, including Alzheimer's disease, frontotemporal dementia, different tauopathies, Parkinson's disease, prion disease, motor neuron diseases such as multiple sclerosis and spinal muscular atrophy. This book provides a clear explanation of different neurodegenerative diseases with new concepts of understand the etiology, pathological mechanisms, drug screening methodology and new therapeutic interventions. Other chapters discuss how hormones and health food supplements affect disease progression of neurodegenerative diseases. From a more technical point of view, some chapters deal with the aggregation of prion proteins in prion diseases. An additional chapter to discuss application of stem cells. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

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