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# Plant polyphenols as natural drugs for the management of Down syndrome and related disorders

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ABSTRACT

Polyphenols are secondary metabolites of plants largely found in fruits, vegetables, cereals and beverages, and therefore represent important constituents of the human diet. Increasing studies have demonstrated the potential beneficial effects of polyphenols on human health. Extensive reviews have discussed the protective effects of polyphenols against a series of diseases such as cancer, cardiovascular diseases, diabetes, and neurodegenerative disorders. Limited studies have investigated the potential therapeutic effects of these natural compounds on neurodevelopmental disorders associated with intellectual disability, such as Down syndrome (DS), for which mitochondrial dysfunctions and oxidative stress are hallmarks and contribute to the deleterious symptoms and cognitive decline. This review, starting from the structure, source, bioavailability and pharmacokinetics of relevant polyphenols, highlights recent studies on the effect and potential molecular mechanism(s) of action of the phenolic compounds epigallocatechin-3-gallate, resveratrol and hydroxytyrosol in restoring mitochondrial energy deficit and in reversing phenotypical alteration in DS. The clinical implications of plant polyphenol dietary supplements as therapeutic tools in managing DS and other intellectual disability-related diseases, is also discussed.



**Contents**



*Abbreviations:* AD, Alzheimer's disease; AMPK, AMP activated protein kinase; Aβ, beta-amyloid; CRM, curcumin; DS, down syndrome; DSCR1, down syndrome critical region 1; DYRK1A, dual-specificity tyrosine (Y)-phosphorylation regulated kinase 1A; EGCG, epigallocatechin 3-gallate; MeHT, homovanillyl alcohol; MAO, monoamine oxidase; HT, hydroxytyrosol; ID, intellectual disability; TFAM, mitochondrial transcription factor A; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PKA, protein kinase A; QRC, quercetin; ROS, reactive oxygen species; RSV, resveratrol; RTT, rett syndrome; Sirt1, sirtuin-1; SOD1, superoxide dismutase 1; TBI, traumatic brain injury.

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## 1. Introduction

Down Syndrome (DS) is the most common chromosomal abnormality. About 95% of affected individuals have the free trisomy of human chromosome 21 i.e. an extra copy of chromosome 21, and their chromosome count is 47. The leading cause of trisomy is attributed to meiotic nondisjunction which occurs mainly in the ovum although the reason for this phenomenon is not completely clear (Hultén et al., 2010). Indeed, the maternal origin for trisomy of chromosome 21 is prevailing being less than 10% the cases of paternal origin and the maternal age plays a major risk factor on the onset of DS (Coppedè, 2016).

Clinically, DS is a neurodevelopmental disease and the most frequent genetic cause of intellectual disability characterised by symptoms of premature aging as well as cognitive decline (Grieco et al., 2015; Hamlett et al., 2016). The characteristic features of DS are atypical craniofacial profile composed of a combination of epicanthic folds, flat facial projections and protruding tongue. Affected persons have from mild to severe mental retardation and IQ varies between 25 and 50. Congenital malformations are deleterious and debilitating. Approximately 40% of patients with DS suffer from congenital heart defects, immune disorders and increased susceptibility to infection. Moreover DS patients have higher incidence of obesity, diabetes mellitus and lymphoblastic and myeloid leukaemia than healthy people (Van Cleve and Cohen, 2006; Van Cleve et al., 2006).

In recent years, a large number of cytogenetic studies has been conducted, but the mechanism(s) by which this aneuploidy produces the clinical phenotype and induces cognitive impairment has not been fully elucidated. In DS, on the long arm of chromosome 21 the overexpression of specific genes (i.e. the dual-specificity tyrosine (Y)-phosphorylation regulated kinase 1A (DYRK1A) and Down Syndrome Critical Region 1 (DSCR1 or RCAN1) genes), have been linked to the complex metabolic derangement observed in DS (Rachidi and Lopes, 2007). Several studies have also identified nutritional deficiencies in DS population resulting from imbalance in biochemical pathways, due to overexpression of other chromosome 21 genes and their targets. A metabolic derangement of the homocysteine/folate/transulfuration pathways and abnormal DNA methylation have been observed in children with DS involving cystathionine beta-synthase (CBS) and the folate transporter RFC1 genes (Gueant et al., 2005; Iacobazzi et al., 2014).

As well, impaired mitochondria and altered homeostasis of reactive oxygen species (ROS), and oxidative stress have been associated with DS pathogenesis and in the aetiology of other intellectual disability (Valenti et al., 2014). Oxidative stress is believed to be due to an imbalance between the chromosome 21-encoded superoxide dismutase 1 (SOD1) and glutathione peroxidase activities (Rodríguez-Sureda et al., 2015) as well as mitochondrial respiratory chain dysfunctions (Valenti et al., 2011). Alteration in signalling pathways, including cAMP-dependent protein kinase A (PKA) phosphorylation, NAD-dependent sirtuin-1 (SIRT1) acetylation and AMP-activated protein kinase (AMPK)-dependent phosphorylation, have also been associated with impaired redox metabolism and mitochondrial dysfunction in cells isolated from both DS patients and murine models of DS (Valenti et al., 2016; Zuo et al., 2014).

Although the overall prognosis of DS has increased over the last decade due to advances in treatment against infections, DS remains uncured. The majority of patients that reach middle ages develop histopathological and neurochemical features which mimic Alzheimer's disease (AD) and related dementias (Dick et al., 2016). On this basis, the molecular basis of DS has been investigated in the hope of increasing our understanding of the neurobiology of AD and identifying efficacious drug targets.

Over the last two decades, there has been a growing interest for the use of naturally occurring plant-based polyphenolic compounds for the treatment of several degenerative diseases due to their potent therapeutic effects such as antimicrobial, anticancer, antioxidant and anti-inflammatory activities both *in vitro* and *in vivo*. The favourable safety profile of polyphenolic compounds represents another important advantage of these bioactive molecules. Several studies have shown that polyphenolic compounds possess potent neuroprotective effects under both *in vitro* and *in vivo* conditions (Daglia et al., 2014; Nabavi et al., 2014, 2015). Of these compounds, flavonoids are thought to be highly bioactive and are found in several plants (Hwang et al., 2012; Nabavi et al., 2012; Vauzour et al., 2013). However, the commercialisation of these compounds is limited because only one in thousand lead molecules can be developed as a successful drug (Sharma and Gupta, 2015; Molinari, 2009). Newer systematic and scientific approaches are necessary for the development of active drugs derived from plants. Moreover, extracting large amounts of compounds from natural sources remains a challenge, and requires the development of newer biotechnology approaches and total organic synthesis (Atanasov et al., 2015). Despite these shortcomings, current research suggests that natural products are likely to represent a major source of new drugs in the future.

Numerous studies have examined the clinical effects of polyphenolic compounds in neurodegenerative pathologies such as AD, supporting the notion that the neuroprotective properties of these natural molecules can suppress neuroinflammation and potentially enhance memory, learning and cognitive functions (Libro et al., 2016; Pérez-Hernández et al., 2016).

Herein, we focus on recent discoveries concerning the biological effects of plant polyphenols on DS. Emphasis will be given to resveratrol, epigallocatechin-3-gallate (EGCG), and hydroxytyrosol, whose molecular mechanisms underlying their neuroprotective actions extend beyond their usual well-established antioxidant and anti-inflammatory activities. We also review studies which analyze the effects of other polyphenols exerting protection in neurological diseases associated with cognitive impairment. To give a complete picture of the selected polyphenols, their chemistry, bioavailability and studies aimed to improve their pharmacokinetic parameters will also be examined.

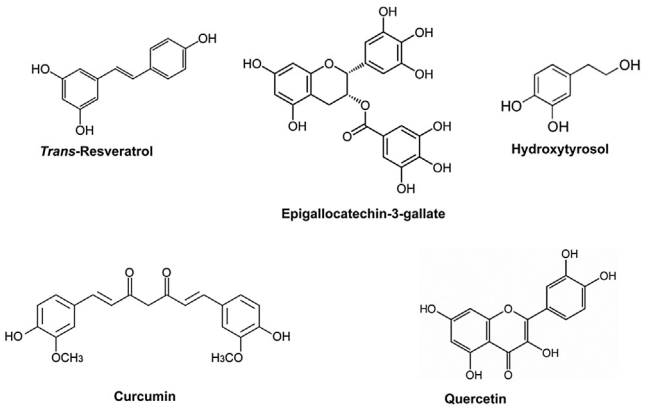


**Fig. 1.** Chemical structure of trans-resveratrol, epigallocatechin-3-gallate, hydroxytyrosol, curcumin and quercetin.

## 2. Polyphenols – miracle compounds in a bowl of salad

Polyphenols are secondary metabolites produced by plants in response to environmental stress or injury, and are important constituents of human diet, since they are present in many plant-derived foods and beverages including fruits, vegetables, cereals, olive, legumes, chocolate, tea, coffee, and wine (Tsao, 2010). Increasing scientific evidence has suggested that daily consumption of foods and beverages rich in polyphenols induces positive effects on human health, and associated with protection against the development of several chronic diseases such as cardiovascular diseases, neurodegenerative diseases, diabetes, osteoporosis, inflammation and several forms of cancer (Fantini et al., 2015; Grootaert et al., 2015).

Examples of well established dietary polyphenols acting on human health and their chemical structures are depicted in Fig. 1: resveratrol (RSV, 3,5,4-trihydroxystilbene) a stilbenoid present in many plants and fresh fruits (including grapes, blueberries, and raspberries) (Aires and Delmas, 2015); epigallocatechin-3-gallate (EGCG), a flavan-3-ol esterified with gallic acid, occuring in tea (*Camellia sinensis L.*), especially in non fermeted teas such as white and green teas (Chowdhury et al., 2016); hydroxytyrosol (HT, 3,4 dihydroxyphenylethanol) a phenylethanoid, the major polyphenol in olive oils (Granados-Principal et al., 2010); quercetin (QRC, 3,3′,4′,5,7-pentahydroxyflavone) a main dietary flavonoid, mainly present in onions and broccoli, but also in seeds, nuts, tea, and red wine (D'Andrea, 2015); curcumin (CRM, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) a diarylheptanoid extracted from the rhizome of *Curcuma longa L.* (Yallapu et al., 2015).

Available literature suggests that mitochondrial dysfunction and the resulting increased levels of free radicals critically impairs the central nervous system leading to loss of neuronal function and survival, which are susceptible to mitochondrial energy deficits and highly reactive free radicals (Rugarli and Langer, 2012; Xavier et al., 2015). Therefore mitochondrial dysfunction has a pivotal role in the pathogenesis of neurodegenerative and neurodevelopmental diseases associated with intellectual disability (ID) (Grimm et al., 2016; Valenti et al., 2014), which leads to deficit or decline in adaptive behaviours and cognitive functions. Interestingly, all the above listed plant polyphenol compounds exert their actions by affecting mitochondrial functions and ROS production, either directly, or by modulating signalling pathways, which regulate mitochondrial functions and ROS homeostasis.

## 3. Source and pharmacokinetic properties of relevant polyphenols

The term "polyphenols" is used to describe aromatic compounds formed by the various shikimate/acetate biosynthetic pathways and their derivatives. Early literature indicated them as "vegetable tannins" used in tanning of animal hides to make leather because their ability to cross-link proteins. Today, this is a wide term indicating vegetable natural antioxidants irrespective of their water solubility, molecular weight or number of phenolic groups (Quideau, 2006).

Over the last two decades, many physiological and pharmacological properties have been ascribed to polyphenols against a large variety of acute and chronic diseases. Polyphenols can exert these protective effects as antioxidants for their capability to react with ROS neutralizing their chemical reactivity. They are transformed by one-electron oxidation in stable radicals that can form dimers or more complex oligomers. The number and position of the hydroxyl phenolic groups mainly confer the stabilization of the radical in polyphenols. Moreover, their antioxidant activity has been attributed to the capacity of inhibiting pro-oxidant enzymes including cyclooxygenase, and lipoxygenase (Hussain et al., 2005; Naasani et al., 2003; Sadik et al., 2003; Yang et al., 2013). Recent studies have shown that polyphenol could act through an epigenetic mechanism of action being able to modulate the expression levels of several important miRNAs (Curti et al., 2014; Gracia et al., 2016; Yu et al., 2015), and through the interaction with signal transduction pathways and cell receptors (Kubota et al., 2009; Nabavi et al., 2016).

Stilbenoids represent an important class of polyphenolic compounds, the most cited of them is trans-resveratrol, phenolic alcohols (i.e hydroxytyrosol and tyrosol), and the large family of flavonoids. Six major subclasses of flavonoids, namely anthocyanidins, flavanols, flavanones, flavones and isoflavones and flavonols, are widespread in the human diet. For example, cyanidine is found in red and purple berries and red wine, flavanols are present as monomers (catechins and epicatechins) and their gallate derivatives such as epigallocathechin-3-gallate, are found in teas (particularly white or green), flavonols as quercetin are found in onions and broccoli, flavones such as apigenin are found in parsley and thyme, flavanones such as naringenin are found in grapefruits and sour orange, whereas isoflavones including genistein are found in soybeans and legumes.

Data regarding the daily polyphenol intake is limited due to the lack of databases reporting food content. Taguchi et al. showed that the average total polyphenol intake in Japanese elderly was about 1.5 g/day, with a great variability among individuals (183–4854 mg/day) (Taguchi et al., 2015). Besides the daily intake, the systemic bioavailability of polyphenols is an important factor that should be considered to evaluate the effectiveness of dietary polyphenols in disease prevention and management. In addition, an equilibrium between metabolism and transport in the cells is related to the circulating concentration and to the type of cells (Maier-Salamon et al., 2013).

## 4. Bioavailability of polyphenols – how to overcome this and other possible pitfalls

Some studies support the poor bioavailability of polyphenols in systemic circulation because of their rapid metabolism and their poor passage through blood brain barrier. In addition, many pathways and mechanisms considered for mediating the neuroprotective action of polyphenols are rather general than specific, showing a broad spectrum of responses both in glial and neuronal cells (Ebrahimi and Schluesener, 2012). Although there are many

**Table 1**
Approaches to improve polyphenols bioavailability.

| Strategies | Examples | Type of polyphenols | Refs |
|---|---|---|---|
| Polyphenols combinations | +piperidine<br>+ginseine<br>+quercetin | EGCG, RSV | Lambert et al., 2004; Wang et al., 2012; Johnson et al., 2011 |
| Combination with other nutrients | Ascorbic acid, selenium, N-acetyl cysteine<br>Fish oil | EGCG, RSV | Gawande et al., 2008; Giunta et al., 2010 |
| Encapsulation | Cyclodextrins<br>Liposome<br>Chitosan-coated nanoliposomes | EGCG, RSV, QCT | Zhang et al., 2013; Das et al., 2008; Frozza et al., 2010 |
| Prodrugs | Polydatine<br>Pro-EGCG | RSV, EGCG | Ji et al., 2012; Pace et al., 2015; Ahmed et al., 2016 |
| Analogs | Structural analogs,<br>methoxylated or glycosylated compounds | RSV, EGCG | Latruffe et al., 2012; Chen et al., 2012 |
| Alternative to oral delivery | Percutaneous<br>Transdermal | EGCG, RSV, HT | Lambert et al., 2006; Hussain et al., 2013 |

*in vivo* and *in vitro* investigations on neuroprotective effects of polyphenols, their pharmacokinetic properties (ADME, Absorption, Distribution, Metabolism, Elimination) have not been fully elucidated. The discussed health effects of natural polyphenols depend mainly on their bioavailability. After oral intake and absorption, polyphenols undergo extensive enzymatic modifications, which lead to the synthesis of glucuronidated, methylated and sulphated compounds at intestinal and liver levels (D'Archivio et al., 2010). Indeed, cells recognize plant polyphenols as xenobiotic compounds that are quickly enzymatically modified in order to eliminate them. For example, the clinical administration of curcumin is limited due to poor solubility and limited adsorption in the gastrointestinal tract, its rapid metabolism and rapid renal clearance (Gupta et al., 2013). Quercetin is present in foods as various glycosides, which are more bioavailable than the free aglycone (quercetin itself) because of efficient deglycosylation process at the intestinal level (Russo et al., 2012). The poor bioavailability of the aglycon form due to lowered absorption in the gastrointestinal tract raises a question of the clinical translation of quercetin.

The bioavailability and the pharmacokinetics of plant polyphenols can be employed to potentially enhance the delivery of polyphenols and optimize their efficacy in humans (see Table 1).

### 4.1. Epigallocatechin-3-gallate

EGCG is the most common bioactive catechin present in green tea. The portion that is not degraded during digestion (Marchese et al., 2014) is adsorbed at the intestinal level through epithelial cells. Afterwards, it is metabolized in the liver to give glucuronide and sulfide metabolite and, especially, methylated metabolites (Yong Feng, 2006). In the blood, EGCG has been found to be methylated, as reported by Meng and co-workers. The human plasma peak concentrations of EGCG and its methylated form were about 145 and 20 nM, respectively, after 2 h following green tea ingestion. After 24 h, the urinary excretion of EGCG methylated derivative was found to be approximately 140 μg, corresponding to about 0.1% of the ingested EGCG (Meng et al., 2002). Although the bioavailability of EGCG is poor due to the degradation occurring during digestion, poor absorption, and rapid metabolism and excretion, EGCG is a promising substance. In addition, it has been found to cross blood-brain-barrier, which is a prerequisite for the efficacy of EGCG against neurodegenerative disorders (Li et al., 2012; Lin et al., 2007).

Considering the beneficial properties of EGCG and its low bioavailability, many recent studies have focused on the search of new delivery forms and combinations of substances to improve its pharmacokinetic properties. One of the earliest studies that addressed the problem was published in 2004 by Lambert et al. The study showed that the combination of black pepper piperine and EGCG (EGCG/piperine 163.8/70.2 μmol/kg) increased the plasma concentration of EGCG by 1.3-fold in comparison with mice treated with EGCG alone. This increase seemed to be caused by the inhibition of EGCG glucuronidation at gastrointestinal levels, thus slowing its metabolism (Lambert et al., 2004). The same research group showed that genistein exerted the same effect of piperine in an *in vitro* model system (HT-29 human colon cancer cells) (Lambert et al., 2008). Similar results were achieved by Wang et al. and Kale et al. that showed that co-treatment with quercetin induced an increase in EGCG bioavailability (Kale et al., 2010; Wang et al., 2012). The possibility of increasing EGCG bioavailability with nutrient combinations was also confirmed in humans by Gawande et al. (2008). The study showed that supplementation of 5 human volunteers with a single dose of green tea catechins, ascorbic acid, selenium, N-acetyl cysteine, and black grapes induced an increase in EGCG bioavailability by 27%. More recently, Giunta et al. reported that in Tg2576 mice the treatment with EGCG (62.5 mg/kg/day or 12.5 mg/kg/day) and fish oil (8mg/kg/day), which induced a statistically significant increase in EGCG bioavailability (Giunta et al., 2010), showed a synergist effect on the inhibition of cerebral beta-amyloid peptide deposits, which are implicated in the pathogenesis of AD. As far as new delivery forms of EGCG are concerned, Lambert et al. reported that transdermal gel, containing EGCG applied on SKH-1 mice epidermis (50 mg/kg), could be an alternative promising form, to deliver EGCG to plasma and tissues, in comparison with the oral form (Lambert et al., 2006). More recently, a number of studies have focused on using nanotechnology to improve EGCG bioavailability; the effect of EGCG encapsulated chitosan-coated nanoliposomes on the intracellular concentration of EGCG in THP-1-derived macrophages and MCF7 breast cancer cells has been reported (de Pace et al., 2013; Zhang et al., 2013). The results showed that these nanoliposomes significantly increase the stability and the concentration of EGCG in the cells, improving also EGCG bioactivities.

Several EGCG analogues have been also developed. Pro-EGCG, a prodrug of EGCG has been shown to demonstrate greater stability, and higher bioavailability and biological activity *in vivo*, in comparison to the naturally derived EGCG (Ahmed et al., 2016). Similarly, compounds 2a and 4a showed lower susceptibility to methylation/inhibition by the catalytic activity of catechol-O-methyltransferase, a key enzyme involved in the metabolism of EGCG (Ahmed et al., 2016). Additionally, these drugs demonstrated potent antiproliferative, antiangiogenic, and antifibrotic activities in human uterine leiomyoma cells *in vitro*. Another study showed that synthetic EGCG analogs 4 and 6 resulted to be more potent AMPK activators than EGCG and metformin, which is the drug commonly used to treat type 2 diabetes. Activation of AMPK by these EGCG synthetic analogs inhibited cell proliferation, induced the over expression of the cyclin-dependent kinase inhibitor p21 and the down-regulation of mTOR signaling pathway, and suppressed

the stem cell population in cells of human breast cancer *in vitro* (Chen et al., 2012). Taken together, these studies suggest that novel EGCG analogs have potential to be used in the clinic, due to their improved bioavailability and increased efficacy against neurodegenerative processes.

### 4.2. Resveratrol

Similarly, RSV is a naturally occurring polyphenol isolated from grapes, red wine, peanuts, berries and other plants such as *Polygonum cuspidatum* Siebold & Zucc (Kurita et al., 2014). Over the last two decades, resveratrol has been studied for its multitude health-promoting effects. Nevertheless, the poor bioavailability put a question mark for its efficacy *in vivo*. RSV is efficiently absorbed, but its rapid and extensive metabolism leads to the formation of metabolites (i.e. glucuronide and sulfate derivatives), which are unstable and are subject to rapid urinary elimination. Indeed, resveratrol concentration in the blood is detected in the nanomolar range (Goldberg et al., 2003). Its physicochemical characteristics (i.e. low water solubility, increased oxidation on heat and light exposure, and low chemical stability) and poor pharmacokinetic parameters has lead researchers to focus their attention on new delivery systems as valid alternatives to overcome these limitations and to reach pharmacologically relevant doses for clinical use. One of the first studies aimed at improving the physicochemical properties of resveratrol showed that the encapsulation of resveratrol in yeast cells increased its solubility, stability to gastroduodenal conditions and its antiradical capacity (Shi et al., 2008). Das et al. (2008) reported that cyclodextrins (i.e. hydroxypropyl-beta-cyclodextrin and randomly methylated-beta-cyclodextrin) increased the water solubility, and improved the absorption of resveratrol, even though the oral bioavailability remained unchanged. More recently, Teskac et al. studied the effect of solid lipid nanoparticles (size below 180 nm), used as a carrier for resveratrol, on several biological and biochemical parameters in keratinocytes (growth, morphology, internalization, and metabolic activity) (Teskač and Kristl, 2010). Frozza et al., loaded resveratrol into lipid-core nanocapsules to increase the distribution of this molecule especially in brain tissue in healthy experimental animals (Frozza et al., 2010). In this study, rats were fed with trans-resveratrol-loaded lipid-core nanocapsules. The brain tissue of the resveratrol-loaded nanocapsules treated animals resulted in a higher concentration of resveratrol and showed less damage in comparison with animals treated with free trans-resveratrol, suggesting the positive influence of this new delivery form on the pharmacokinetics of resveratrol. Similar results were achieved by other more recent investigations on different types of nanoparticles (Cho et al., 2014; Neves et al., 2013; Ramalingam and Ko, 2016; Singh and Pai, 2016; Zu et al., 2016). Another study (Wang et al., 2011) showed that the positive effect of resveratrol on nigral cells isolated from an experimental animal model of Parkinson's disease, was increased by the incorporation of resveratrol into liposomes, thus providing greater protection to rat dopaminergic neurons. The authors ascribed the higher activity of resveratrol liposomes in comparison with the free form, to the higher bioavailability. More recently, Chang et al. considered a new oral delivery system. In more details, they incorporated a grape peel extract (containing high concentrations of resveratrol) into a solid dispersion delivery system with the aim of increasing the water solubility, dissolution and oral absorption of polyphenols present in grape extract (Chang et al., 2016). Furthermore, the skin absorption route is proposed a complementary potent way to achieve therapeutic effects with RSV (Murakami et al., 2014). Interactions with other polyphenols such as piperidine and quercetin potentiate the effects of resveratrol (Castrejón-Tellez et al., 2016; Johnson et al., 2011). Another approach to improve resveratrol delivery is the use of resveratrol precursors, more able then free trans-resveratrol to entry into tissues where they can be metabolize into resveratrol to maximize tissue concentration. It has been shown that the resveratrol prodrug polydatin, a natural glycoside of resveratrol, extracted from the rhizome of *Polygonum cuspidatum*, reduces inflammation through decreasing of NF-κB activation and oxidative stress protecting brain from damage (Ji et al., 2012) and in a pilot clinical study it decreases oxidative stress and improves serum biochemical parameters as well as some cognitive behaviour during chronic alcoholism (Pace et al., 2015). Structural analogs of RSV, such as methoxylated or glycosylated compounds have also been synthesized to obtain higher bioavailability (Latruffe et al., 2012).

### 4.3. Hydroxytyrosol

As far as hydroxytyrosol is concerned, the most important dietary sources of this polyphenol are olives (*Olea europaea* L.) and olive oil. A large body of evidence suggest that olive oil possesses many protective effects against cardiovascular diseases and type 2 diabetes, linked to the capacity to inhibit LDL oxidation, reduce postprandial blood glucose and exert anti-inflammatory activity. All these properties can be ascribed to hydroxytyrosol activity against lipid oxidative damage (Covas et al., 2006).

As regards to the bioavailability of hydroxytyrosol, it is absorbed at intestinal level. Visioli et al. showed that in humans, tyrosol and hydroxytyrosol are dose-dependently absorbed after the consumption of olive oil and the glucuronide conjugates are excreted in the urine. Moreover, they demonstrated that the extent of glucuronidation is directly associated to the ingested amount of phenolic alcohols (Visioli et al., 2000). After absorption, hydroxytyrosol is submitted to a rapid and extensive metabolism favouring the excretion of its metabolites at urinary level, and leading in the whole to a poor bioavailability (less than 10%) (Miró-Casas et al., 2001). In particular, hydroxytyrosol undergoes methylation, glucuronidation, sulphation and thiol conjugation. The hydroxytyrosol sulfate was found to be the main phenolic metabolite quantified in plasma. In addition, hydroxytyrosol acetate sulfate resulted to be the main biological metabolite of hydroxytyrosol (Rubió et al., 2012). As far as hydroxytyrosol tissue distribution, it was found to be distributed through the blood stream to heart, brain, liver, kidney, spleen, testicle and thymus. It resulted to be able to cross the blood-brain barrier suggesting that this polyphenols could exert an *in vivo* neuroprotective activity (Serra et al., 2012).

Despite the poor oral bioavailability, to date the investigations aimed to increase its absorption or to decrease its extensive metabolism are very limited and mainly focused on percutaneous administration for the treatment of atopic dermatitis (Hussain et al., 2013; Siddique et al., 2016).

## 5. Beneficial effects of polyphenols in Down syndrome

Recent studies have shown that polyphenols improve cognitive functions such as memory and help delay or slow age-related cognitive decline (Libro et al., 2016; Pérez-Hernández et al., 2016). Nutritional intervention with the aim to modulate the expression of genes and signalling pathways and to enhance mitochondrial function can be a promising strategy to correct clinical phenotypes associated with increased oxidative stress and energy deficit in DS and could be useful to reduce and delay the pathological clinical signs associated with DS, improving the quality of life of DS persons. Herein, we will focus on polyphenols as nutritional supplementation in DS for their multimodal action in metabolic pathways altered in DS. Indeed, polyphenol compounds interact with cell metabolism influencing maintenance of energy balance through modulation of acetyl CoA/NADPH (Zuo et al., 2014), lipid oxida-

tion (Wang et al., 2015), homocysteine metabolism (Kołodziejczyk et al., 2011) and through inhibition of oxidative DNA damage (Wang et al., 2014). In additions, polyphenols can modulate signal transduction pathways, which regulate mitochondrial functions such as respiration, oxidative phosphorylation and mitochondrial-dependent apoptosis. Polyphenols also regulate ROS homeostasis efficiently scavenging mitochondrial ROS and upregulate antioxidant transcriptional programmes in cells (Gibellini et al., 2015) Notwithstanding this, until now only EGCG, RSV and HT have been tested in DS.

### 5.1. Epigallocatechin-3-gallate in DS: studies in vitro, in animal models and in humans

EGCG is a flavonoid with a very high antioxidant capability; this is due to the presence of more structures that stabilize the phenoxy radical as shown in Fig. 2. Unpaired electron can be delocalized through resonance forms in ortho or para position (2′ or 6′) with respect to the original radical. Indeed, migration of the electron results in three forms for EGCG and in two forms for ECG (epicatechingallate), which lacks the 5′-hydroxyl group in B-ring. Other resonance structures involving radical formation in A-ring and gallate moiety are possible. Abstraction of a second hydrogen atom from a phenoxy radical leads to stable ortho-quinones. Coupling of two of these resonance structures in various combinations gives a range of dimers (Sang et al., 2002). The gallate moiety helps to penetrate the interior of membranes. It has been shown that the relative antioxidant capacity of EGCG is higher with respect to the one of ECG at acidic pH (Costa et al., 2007) and this agrees with our scheme.

EGCG, has been experimented both in clinical trials and in murine models of DS. It resulted a promising candidate for the treatment of DS. EGCG is a specific inhibitor of the kinase activity of the chromosome 21-encoded DYRK1A, an enzyme involved in brain development and in the control of synaptic plasticity (Park et al., 2009). Furthermore, EGCG helps to rescue brain functions and enhance some cognitive phenotypes in Ts65Dn, a mouse model of DS (Souchet et al., 2015; De la Torre et al., 2014). In a recent investigation, euploid and Ts65Dn mice were treated with EGCG from 3 to 15 days postnatal and the response to treatment was determined at its cessation and after one month. The authors reported that treatment with EGCG recovered neurogenesis, total hippocampal granule cell number and levels of pre- and postsynaptic proteins in the hippocampus and neocortex at the end of treatment. However, these beneficial effects were not present after 1 month from treatment cessation, as well as improvement in hippocampus-dependent tasks, thus suggesting that EGCG has no effect on adult hippocampal physiology when administered in neonates (Stagni et al., 2016).

Our previous investigations showed that in human DS cell cultures the efficacy of EGCG in decreasing oxidative stress and mitochondrial energy deficit through a mechanism involving cAMP/PKA and SIRT1 signalling pathways (Valenti et al., 2013) (Fig. 3). A phase I and the following phase II clinical trials have demonstrated that treatment of EGCG of young adults with DS is safe, with a mild positive effects on cognitive performances (De la Torre et al., 2014) but able to potentiate the cognitive training enhancing visual recognition memory, inhibitory control as well as adaptive behaviour (de la Torre et al., 2016). Reasonably, an early EGCG treatment in childhood and increasing its bioavailability could further improve its beneficial effects. Recently, we demonstrated that a dietary supplementation of EGCG in combination with omega-3 fatty acids from fish oil, which enhances EGCG bioavailability and synergize its effectiveness (Giunta et al., 2010), in a DS child is safe, rescues mitochondrial dysfunction already after 1 month-treatment and improves some behavioural deficits after 6 month-treatment (Vacca and Valenti, 2015).

### 5.2. Resveratrol in DS: in vitro studies

RSV is a phytoalexin synthesized by plants in response to environmental stress and interest in this compound started from the “French paradox” in 1982, and an explosion of literature about the impact of it on oxidative-stress related diseases occurred in spite of its lower concentration in red wine compared to the procyanidins and its poor bioavailability (Chachay et al., 2011). Due to its multiple-targets action which includes mitochondria (de Oliveira et al., 2016c), RSV can exert both *in vitro* and *in vivo* a neuroprotective action with potential role in the prevention of various cognitive decline-related neurological disorders including AD (Ahmed et al., 2016; Bastianetto et al., 2015). However, in DS, it has been tested only in one study *in vitro* by our group (Valenti et al., 2016) and never in DS population. We showed that RSV, as well as EGCG, in hippocampal progenitor cells from Ts65Dn mouse model of DS, reverses the serious impairment of mitochondrial bioenergetics and biogenesis, rescuing the *in vitro* impaired neurogenesis with a mechanism of action linked to the activation of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α)/SIRT1/AMPK axis (see Fig. 3). We suggest that resveratrol, beside to EGCG, shows a potential beneficial action for treatment in DS despite it does not interact with DRK1A. It should be noted that RSV downregulates a specific microRNA, the miR-155 (Latruffe et al., 2015). Interestingly, miR-155, triplicated in Down syndrome since encoded by chromosome 21 and overexpressed in DS brain regulates a plethora of genes including mitochondrial genes and controls the nuclear mitochondrial transcription factor A (TFAM) that regulate mitochondrial biogenesis (Quiñones-Lombraña and Blanco, 2015; Wang et al., 2013). Thus, the normalization of miR155 by RSV could be a very interesting strategy to prevent the impairment of mitochondrial biogenesis and other metabolic alterations found in DS.

### 5.3. Hydroxytyrosol in DS: ex vivo studies

Hydroxytyrosol is not strictly a polyphenol since it possesses only a phenolic group, although it still belongs to the group of polyphenol compounds. It is the product of hydrolysis under acidic conditions of oleuropein mainly contained in olive oil and the content of HT increases with curing and processing of olives.

HT and its methoxy analogue homovanillyl alcohol (MeHT) have been studied for the possible protective effect of phenolic antioxidants in DS. These compounds display ROS scavenging activities and metal chelating properties in erythrocytes of DS children, HT being more active than MeHT. Both compounds significantly decrease oxidative stress-induced ROS generation and lipoperoxidation in erythrocytes from DS children (Manna et al., 2012). The intra erythrocyte iron accumulation is a signal of increased Alzheimer’s disease risk in DS (Manna et al., 2012; Prohaska et al., 2012).

It has been also shown that HT regulates mitochondrial biogenesis and oxidative phosphorylation system in fibroblasts and that the positive effect of HT was associated with activation of PKA and the PGC-1α transcription cascade (Signorile et al., 2014) both impaired in DS cells. Therefore, HT is proposed as a good candidate as a novel dietary strategy to produce potential therapeutic benefits in DS (see Fig. 3).

Other plant polyphenols, can be studied for their interaction with protein subunits of mitochondrial respiratory chain complexes. In our opinion, also studies of molecular docking of polyphenols with side groups of amino acids making proteins

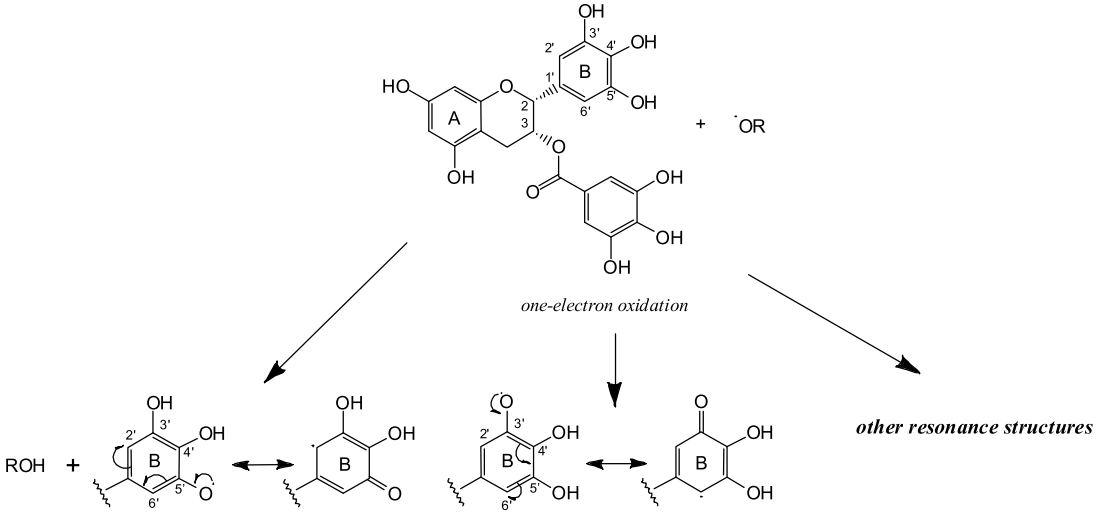


**Fig. 2.** Formation of phenoxy radicals from EGCG and its resonance structures.

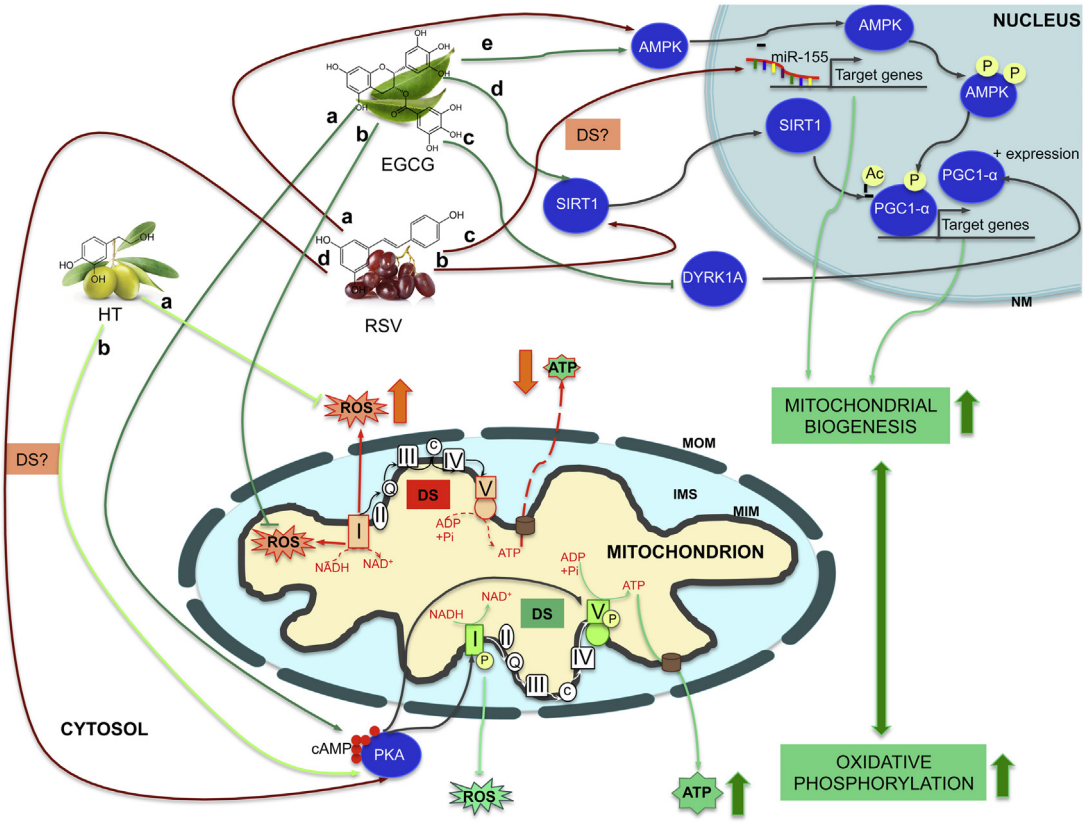


**Fig. 3.** Targets of epigallocatechin-3-gallate (EGCG), resveratrol (RSV) and hydroxytyrosol (HT) in Down syndrome.
In DS cells (DS highlighted in red) an impairment of complex I (I) and ATP synthase (V) activity occurred resulting in mitochondrial ATP synthesis decrease and ROS production increase.
Treatment with EGCG (dark green lines) of DS cells (DS highlighted in green) resulted in: (a) stimulation of cAMP/PKA signalling pathway with consequent increase of PKA-dependent phosphorylation and activities of complexes I and V; (b) scavenging of intramitochondrial ROS produced by the dysfunctional complex I; (c) inhibition of DRK1A activity with consequent increase of PGC1-α expression; (d) activation of SIRT1 with a consequent PGC1-α deacetylation; (e) increase of AMPK phosphorylation and activity with a consequent PGC1-α phosphorylation and activation.
Treatment with RSV (red lines) resulted in: (a) increase of AMPK phosphorylation and activity with a consequent PGC1-α phosphorylation and activation; (b) activation of SIRT1 with a consequent PGC1-α deacetylation. In addition RSV, as in other cell type, could target mirR-155 (c) and increase expression of target genes of mitochondrial biogenesis as well as target (d) cAMP/PKA signalling pathway with consequent increase of PKA-dependent phosphorylation and activities of complexes I and V.
Treatment with HT (light green lines) resulted in: (a) cytoplasmic ROS scavenging and, as in other cell type, could target (b) cAMP/PKA signalling pathway with consequent increase of PKA-dependent phosphorylation and activities of complexes I and V.
Other abbreviations: NM, nuclear membrane; MOM, mitochondrial outer membrane; IMS, mitochondrial intermembrane space; MIM, mitochondrial inner membrane. Respiratory chain complexes: II, complex II; Q, coenzyme Q; III, complex III; *c*, cytochrome *c*; IV, complex IV.

encoded in chromosome 21 overexpressed in Down's syndrome could clarify the mechanism of interaction.

## 6. Beneficial effects of polyphenols by targeting mitochondria in aging and other diseases related to cognitive decline

Targeting mitochondria is a new therapeutic area for alternative-drug treatment of cognitive-associated diseases. Polyphenolic compounds for their role in regulating ROS homeostasis and modulating mitochondrial function could be promising therapeutic tools in diseases linked to mitochondrial dysfunctions and aberrant redox homeostasis (Arun et al., 2016).

Herein we review the mechanisms of action of some polyphenols in cognitive-associated diseases, some of them already analysed for their action in DS.

### 6.1. Resveratrol

Resveratrol reduces aging-dependent cognitive decline and pathology in animal models system of AD exerting effects similar to that registered with caloric restriction (Karuppagounder et al., 2009) and is safe, well-tolerated, and alters some AD biomarker in human (Turner et al., 2015). Dietary supplementation with RSV of animal models have been determined improvement of several mitochondrial functions such as oxygen consumption, activity of respiratory enzymes, and activity of lipid-oxidizing enzymes as well as mitochondrial biogenesis (Murase et al., 2009). Although the exact molecular events by which RSV mediates the improvement of mitochondrial function and exerts neuroprotective action are not known in detail, it likely relies on RSV ability to activate intracellular effectors such as AMPK (Dasgupta and Milbrandt, 2007), an evolutionarily conserved enzyme which senses the lowering of cell energy status and regulates cellular survival with emerging function in neuroprotection (Poels et al., 2009), and SIRT1 an enzyme catalyzing $NAD^+$-dependent protein deacetylation, involved in the modulation of several metabolic transcriptional regulators (Lagouge et al., 2006). Both SIRT1 and AMPK are well known activators of PGC-1α, which in turn improves the transcription of genes involved in the oxidative phosphorylation and biogenesis of mitochondria (Lagouge et al., 2006). RSV has been shown to allosterically interact with SIRT1, thus resulting in the increase of its affinity for both $NAD^+$ and the acetylated substrates (Howitz et al., 2003) and the consequent induction of PGC1α activity by SIRT1-mediated deacetylation. On the other hand, RSV has been shown to induce AMPK phosphorylation in neuronal cell lines, primary neurons and brain (Dasgupta and Milbrandt, 2007; Valenti et al., 2016). The action of RSV on AMPK and SIRT1 impact the phosphorylation/acetylation status of PGC1α and consequently PGC1α activates mitochondrial biogenesis and improves mitochondrial function, an essential step in the whole neuroprotective effect of RSV. Interestingly, several studies indicate that both SIRT1 and AMPK are necessary for the metabolic actions of RSV and that these proteins likely exert their function in concert. Indeed, blocking either AMPK or SIRT1 prevents RSV-induced mitochondrial biogenesis *in vivo* (Kulkarni and Cantó, 2015). Another important point is RSV-mediated protection of neuronal cells against beta-amyloid (Aβ)-induced neurotoxicity. RSV likely interferes in Aβ protein aggregation and lowers Aβ levels and plaques, in a process probably involving the RSV-dependent activation of protein kinase C (PKC) isoforms and AMPK (Bastianetto et al., 2000). The above-mentioned multimodal action of RSV can explain the observed ability of RSV to extend life span and to play protective function against metabolic and neurological diseases.

However, adverse effects and limited efficacy have also been reported in a randomized, placebo-controlled multicenter phase 2 trial with RSV in patients with mild to moderate AD, conducted to verify its safety and tolerability. Moreover, the effects on some biomarker (plasma Aβ40 and Aβ42, CSF Aβ40, Aβ42, tau, and phospho-tau 181), volumetric MRI outcomes (used as primary outcomes) and clinical outcomes (used as secondary outcomes) were studied (Turner et al., 2015). The most common adverse events reported in the resveratrol-treated group were gastrointestinal symptoms such as nausea, diarrhea, and weight loss. CSF Aβ40 and plasma Aβ40 levels were reduced more in the placebo group than the resveratrol-treated group; as well brain atrophy was increased in the resveratrol group compared to the placebo group. Further studies are warranted to elucidate the effects of resveratrol treatment on trajectories of AD biomarkers.

### 6.2. Epigallocatechin-3-gallate

EGCG has been shown to be a multipotent therapeutic agent with beneficial neuroprotective effects not only in DS, but also in other intellectual disability-related diseases, such AD. The potent neuroprotective role of EGCG derives essentially from its ability to act as an anti-oxidant molecule when administered at relatively low concentrations, and to target mitochondria and signalling pathways controlling mitochondrial functions. It should be stressed that EGCG can also exert pro-oxidant effects at higher concentrations, and these properties have been used in cancer therapy for inducing cancer cell death (de Oliveira et al., 2016b; Valenti et al., 2013). As a mitochondrial-targeted molecule, EGCG exhibits the ability to maintain mitochondrial function in conditions of neurotoxicity, among which amyloid-induced toxicity. In particular, EGCG was found to restore respiration rate, mitochondrial membrane potential and ATP levels and to reduce ROS production both in hippocampus, striatum and cerebral cortex of a mouse model of AD in which has been shown to decrease Aβ levels and plaques by promoting the antiamyloidogenic β-secretase proteolytic activity, and to remodel α-synuclein amyloid fibrils into disordered oligomers, respectively (Chowdhury et al., 2016; Dragicevic et al., 2011).

Similarly, in vitro studies (in cultured astrocytes and neurons) showed that EGCG has been shown to increase ATP production by mitochondria, with different kinetic parameters and without toxicity, likely by activating cytochrome C oxidase (Castellano-González et al., 2016). In other studies, EGCG was shown to prevent mitochondrial dysfunction occurring in aged rat brain (Srividhya et al., 2009) and to exert a protective effect in toxic pollutant (cadmium)-induced mitotoxicity, *in vitro*, probably due to its antioxidant and chelating effects, finally countering mitochondrial dysfunction and lipid peroxidation (Abib et al., 2011). As RSV, also EGCG has the capacity to activate or inhibit various cellular signalling pathways, among which SIRT1 and AMPK (Valenti et al., 2016, 2013).

Additionally, EGCG has been shown to attenuate oxidative stress by modulating autophagic processes to reduce lipid accumulation. EGCG treatment induced an increase in the generation of LC3-II and autophagosomes in primary bovine aortic endothelial cells (Kim et al., 2013). Moreover, the same study suggested a potential mechanism of action. In fact, the study reported that the activation of calmodulin-dependent protein kinase β was necessary for LC3-II formation induced by EGCG. Moreover, the EGCG treatment also attenuated palmitate-induced lipid accumulation, by stimulating autophagy. Inhibition of autophagosomal degradation reversed the beneficial effects of EGCG in ectopic lipid accumulation. Results of this study suggest that EGCG mediates protective effects by enhancing autophagic flux. Using ATG5 small interfering (si) RNA and autophagy inhibitors, another study recently showed that EGCG exerts protective activity against human prion protein-induced damage of neuronal cells through inhibition of Bax and cytochrome

c translocation (Lee et al., 2015). The study further showed that the beneficial effects of EGCG on autophagic pathways in neurons were dependent on SIRT1 activation. Taken together, these results induce to speculate that EGCG may be a potential therapeutic agent in neuroinflammatory conditions where there is marked evidence of disrupted autophagy.

### 6.3. Quercetin

Another polyphenol with potential health benefits and protective effects against neurological diseases is quercetin. This bioflavonoid can improve mitochondrial function and structure through modulation of mitochondrial biogenesis and respiration, redox signaling as well as energy production (de Oliveira et al., 2016a). QRC protects mitochondria against the damages caused by several cellular stressors. In addition, it was found to be effective in the modulation of serotonergic action by reducing mitochondrial monoamino oxidase (MAO) activity in the brain, thus attenuating hydrogen peroxide generation accompanying the reaction of MAO (Yoshino et al., 2011). QRC supplementation was also effective in improving mitochondrial dysfunctions in 3-nitropropionic acid induced rat model of Huntington's disease through inhibition of respiratory chain complexes, restoring of ATP levels and preventing mitochondrial swelling, thus ameliorating mitochondrial dysfunctions, oxidative stress and neurobehavioral deficits (Sandhir and Mehrotra, 2013). Finally, a recent study showed that QRC reduces aluminum-induced mitochondrial swelling, loss of cristae and chromatin condensation and decreases ROS production and increases mitochondrial superoxide dismutase activity acting as an effective antioxidant *in vivo* against aluminum-induced neurodegeneration in rat hippocampus (Sharma et al., 2016).

### 6.4. Curcumin

Curcumin is a phenolic compound occurring in turmeric (*Curcuma longa*) as a yellow pigment, is a promising compound for its potentially helpful nutraceutical properties in the prevention of mitochondrial dysfunction. Curcumin is an antioxidant compound able to react directly with ROS and to induce the expression of cytoprotective and antioxidant proteins through the transcription factor nuclear factor-erythroid-2-related factor 2 (Nrf2) (Trujillo et al., 2014). CMN also attenuates the effects of chronic administration in mice of D-galactose-induced cognitive impairment, oxidative stress as well as mitochondrial dysfunction (Kumar et al., 2011). Moreover, curcumin mitigates oxidative stress and alleviates cognitive dysfunction in patients with AD, as well as reduces amyloid accumulation among the neuronal tissues in animal models of AD (Baum et al., 2008). Dietary QRC administration remarkably restored the aging-related cerebrovascular via the up-regulation of AMPK pathway (Pu et al., 2013).

CMN supplementation was shown to be an effective therapy to reduce the negative effects on homeostatic control of energy balance and cognitive function of traumatic brain injury (TBI), often reducing cognitive ability (Sharma et al., 2009). Dietary CMN is a safe treatment useful in the management of TBI patients with functional restoration.

As far as neurodevelopmental diseases, in propanoic acid-induced autism rats, a model of autism, CMN was found to restore the associated symptoms of autistic phenotype by suppressing oxidative-nitrosative stress and mitochondrial dysfunction (Bhandari and Kuhad, 2015), therefore, it is proposed as a potential neuropsychopharmaco-therapeutic adjunct for autism spectrum disorders. Also for Rett syndrome (RTT) – a severe neurological disorder, one of the leading cause of ID in female, associated with oxidative stress and mitochondrial dysfunction (De Filippis et al., 2015) – it has been shown that dietary supplementation with curcumin in a mouse model of RTT reduces intravascular ROS overproduction and reverses alterations critical for RTT (Panighini et al., 2013).

### 6.5. Hydroxytyrosol

HT is a phenolic alcohol occurring in olive oil able to reduce oxidative stress and improve mitochondrial function. In murine-dissociated brain cells, an extract rich in HT resulted to attenuate $Fe^{2+}$- and nitric oxide-induced cytotoxicity associated with a severe loss of cellular ATP and a markedly depolarized mitochondrial membrane potential (Schaffer et al., 2007). In the same study mice feeding experiments were performed to assess the brain bioactivity of HT *ex vivo*. Sub-chronic administration of HT (100 mg/kg body weight) for 12 days ameliorates the resistance of dissociated brain cells to oxidative stress, as shown by reduced basal and stress-induced lipid peroxidation. Also, basal mitochondrial membrane potential was moderately hyperpolarized, an effect suggestive of cytoprotection. In synthesis, the *ex vivo* data provide the first evidence of neuroprotective effects of oral HT intake or supplementation (Schaffer et al., 2007).

The neuroprotective effects of HT have been shown on a commonly used model system of prenatal restraint stress which induces long-lasting neurobiological and behavioural alterations, including altered neuroplasticity and cognitive dysfunction (Zheng et al., 2015). Oxidative stress and mitochondrial impairment in prenatally stressed rats were reported with abnormalities in protein oxidation, SOD activity, decreased expression of mitochondrial complexes and copy number of mitochondrial DNA. Maternal supplementation with high-dose HT significantly increased levels of overall mitochondrial respiratory complex components compared to the stress group and mitochondrial DNA copy number. Similarly, the learning and memory impairment induced by prenatal stress in both male and female offspring were found significantly modified in the HT supplement groups thus, indicating HT as an effective nutritional supplement ameliorating neurogenesis and cognitive function in prenatally stressed offspring (Zheng et al., 2015).

## 7. Concluding remarks

In this review we have shown as plant polyphenols, affecting a multitude of functions that have been correlated with the biology of the mitochondria, exert positive effects for development and function of neurons (see Fig. 4). Therefore, dietary supplements with plant polyphenol compounds may have important neuroprotective effects in preventing or managing some diseases associated with intellectual disability for which brain mitochondrial dysfunctions and oxidative stress are critical. Food supplements used earlier instead of later during development could be more effective in enhanching cognitive outcomes (Stagni et al., 2015). For instance, brain alterations and mitochondrial dysfunctions are already present prenatally in patients with DS (Olmos-Serrano et al., 2016; Valenti et al., 2011) as well as errors in the metabolism of some aminoacids, particularly Glutamate/Glutamine ratio (Amorini et al., 2012). Therefore, polyphenol extracts, for their safety, efficacy in reversing critical alterations in DS, should be considered for therapeutic interventions in early childhood or the prenatal period to rescue brain development and prevent cognitive behaviour impairment; EGCG can cross the blood-brain and feto-maternal placental barriers (Martel et al., 2010). For example EGCG administered at neonatal and embryonic life stages in the Ts65Dn mouse model of DS, fully restores hippocampal neurogenesis but not in adulthood (Stagni et al., 2016) thus suggesting a long-term assumption of this polyphenol. We also suggest that the use of these phytochemicals early during development associated with other therapeutic agents

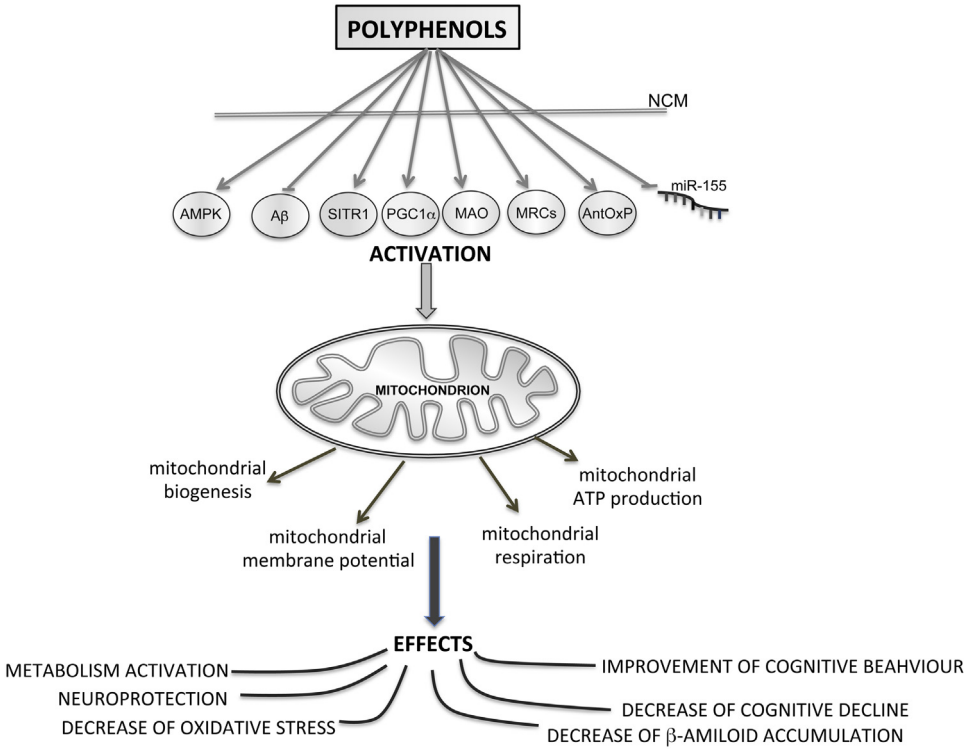


**Fig. 4.** Suggested model of polyphenols molecular action in neural cells.
Treatment with plant polyphenols leads to activation/inhibition of a variety of signalling proteins. Activation of AMPK, SIRT1, PGC1α, monoamino oxidase (MAO), antioxidant proteins (AntOxP) and mitochondrial respiratory chain complexes subunits (MRCs), and inhibition of beta-amiloid protein (Aβ) and miRNA155 (miR155) induce an improvement of several mitochondrial functions and in turn beneficial effects in central nervous systems. NCM, neuronal cytoplasmic membrane.

may lead to the better cognitive outcome in complex neurodevelopmental disorders.

However, some lines of research should be explored prior to a systematic use of these natural compounds in the clinical practice such as dose-response relationship and strategies directed at improving their bioavailability. Also, rigorous studies on large cohorts of subjects in the different intellectual disability-linked neurological diseases are needed to clearly define the effects of these natural compounds in ameliorating cognitive behaviour of individuals with intellectual disability.

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