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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.