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INTRICACIES IN TRISOMY 21; ROLE OF CERTAIN POLYPHENOLS IN COGNITIVE DYSFUNCTION ALLIED WITH NEURODEGENERATION

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ABSTRACT: One of the most prominent issues with Down Syndrome (DS) individuals is the cognitive deficits that come with early-onset Alzheimer's disease (AD). Numerous mechanisms are accountable for neurodegeneration and declined cognition, including impairment in neurogenesis leading to hypocellularity in the cortex, cerebellum and hippocampus, altered dendritic morphology, and altered synapses plasticity. Pharmacotherapy is typically based on stimulating the proliferation of the neuronal count. Previously it has been hypothesized that mitochondrial dysfunction followed by an increase in the levels of free radicles plays a critical role in the impairment of the CNS, which results in a loss of neuronal function and viability. And Hence, mitochondrial dysfunction can be portrayed as a major cause in the pathogenesis of neurodegenerative disorders associated with cognitive deficits. There is a rising curiosity about the potential of the natural polyphenol compounds for improving memory and learning and also the general cognitive capability and reversing the age-related declinations. The polyphenols act by directly affecting the mitochondrial dysfunction or modulating the cellular signaling pathways that regulate the mitochondrial functions and ROS homeostasis.

INTRODUCTION: Down Syndrome (DS) or Trisomy 21 is the most widespread genetic disorder and a leading cause of mental retardation. The incidences in India are about 1 per 700-800 live births. Down syndrome patients show the occurrence of a third copy of chromosome 21 and this additional genetic material roots the developmental vicissitudes and physical topographies of Down syndrome.

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The superfluous chromosome is mostly derived from the mother in about 93% of the cases, and this is mainly due to anomalous chromosome segregation or nondisjunction during meiosis [1]. The phenotypes allied with DS comprise symptoms that distress multiple bodily functions, mostly the musculoskeletal, cardiovascular systems, and neurological complications.

DS patients are commonly diagnosed with short stature, cognitive dysfunction, atlantoaxial instability (AAI), muscle hypotonia, memory impairment, decreased neuronal density, intellectual incapacity, Brain or cerebellar hypoplasia, and also inherited heart diseases [2, 3]. One of the most prominent issues with DS

individuals is the cognitive deficits and early-onset Alzheimer's disease [4].

Drugs Affecting the Cognitive Decline and Neurodegeneration: Down syndrome individuals also exhibit an age-associated degeneration of the neuronal cells in many regions of the brain, which includes the Locus Coeruleus (LC) & also the basal forebrain. This mainly consequences in a deficit of vital neurotransmitters like Acetylcholine (Ach) & Nor Epinephrine (NE). Furthermore, the rise in expression of the Amyloid Precursor Protein (APP), whichnormally exists in 3 copies in human beings with DS and the Ts65Dn model grounds an associated intensification in the APP derived Amyloid β or Aβ peptides, which then forms the utmost important element of "Amyloid Plaque" in Alzheimer's disease. Aβ might also promote cognitive declination in Down syndrome by persuading a synaptic depression in the neuronal cells that overexpress the Amyloid precursor protein (APP), or neurotoxicity induced mainly by oxidative stress [5].

Likewise, for the animal models of Alzheimer's Disease, an age-associated deterioration of the Locus Coeruleus followed by the reduction of Nor Epinephrine levels is perceived in the Ts65Dn model, along with an increase in production the APP protein. However, it was found that the Ts65Dn mice model does not show any senile plaque deposits and neurofibrillary tangles. The Drugs that alleviate Nor Epinephrine deficiency or the drugs that inhibit the overexpression of the APP proteins have shown promising results in the models of Down syndrome.

L–Threo Dihydroxyphenylserine (L DOPS) has been found to help produce Nor Epinephrine in the Ts65Dn mice model. L DOPS is transformed to Nor Epinephrine with the help of the enzyme Aromatic L amino Acid Decarboxylase (AAD), also known as DOPA Decarboxylase. When being administered along with Carbidopa, L DOPS inhibits the peripheral AAD activities but cannot get past the Blood-Brain Barrier found to restore the learning and memory capabilities in the Ts65Dn model. This enhancement of cognitive behavior has been ascribed to the improved Nor Epinephrine controlled adrenergic stimulation in the hippocampus [5].

Polyphenols and Their Role in Neurodegenerative Assuagement: Polyphenols are a structural class comprising natural, synthetic, semisynthetic and organic chemical agents that consist of multiple sums of phenolic structural elements. Since the last few decades, there has been a surge in the incorporation of several herbal grounded polyphenolic compounds to mitigate various neurodegenerative disorders since it possesses several therapeutic effects like antioxidant, anti-inflammatory, *etc*. Several studies have also shown the neuroprotective potent impact that polyphenolic compounds possess [6]. Fruits and vegetables are the most abundant source of polyphenols in the average human diet. These substances are secondary metabolites of plants and can serve various functions, including metabolic intermediates, reproductive attractants, and protective agents.

Most of these molecules have a high antioxidant capacity and several other important activities that can affect human health, the most important of which appear to be anti-inflammatory properties and the potential ability to modulate different cell signaling pathways [7]. Herein we solely focus on reviewing a certain number of polyphenolic compounds incorporated for the assuagement of neurological disorders associated with cognitive impairment. Previously it has been hypothesized that mitochondrial dysfunction followed by an increase in the levels of free radicles plays a critical role in the impairment of the CNS, which results in a loss of neuronal function and viability. And hence, mitochondrial dysfunction can be portrayed as a significant cause of the pathogenesis in neurodegenerative disorders allied with cognitive deficits. Polyphenolic compounds mainly exert their action by directly affecting the mitochondrialdysfunction or moderating the cellular signaling pathway that regulates the various functions of mitochondria and ROS homeostasis [6, 8, 9].

Epigallocatechin 3 Gallate (EGCG): EGCG is a catechin that is most abundantly present in green tea. After administration, it does not get degraded during the process of digestion; instead, it gets absorbed in the intestine region by the epithelial cells. Later, its metabolism occurs in the liver, and the formation of sulfide, glucuronide metabolites,

and methylated metabolites occurs. In the bloodstream, normally, the EGCG is found in methylated forms, and the peak plasma concentration of EGCG with its methylated forms is nearly around 145 and 20 nM naturally, after about 2 hours of green tea administration. Subsequently, after about 24 hours of ingestion, the urinary elimination or excretion of EGCG and its derivatives were nearly found at around 140 µg, which parallels around 0.1% EGCG of the total ingested [6, 10, 11].

Even though the bioavailability of EGCG isn't good due to its degradation that occurs during digestion, it has relatively poor absorption and rapid metabolism. But one of the most important factors to consider is that EGCG has been discovered to pass through the blood-brain barrier, which is considered a major benchmark for the effectiveness of EGCG against neurodegeneration. One of the studies showed that EGCG, when given in combination with fish oil in the TG2576 mouse model, induces a significant increase in EGCG bioavailability, which shows potent synergistic consequence on the inhibition of cerebral beta-amyloid protein compounds embroiled in the pathogenesis of Alzheimer's disease [12, 13].

Resveratrol: Resveratrol (RSV) is a stilbenoid and a type of naturally occurring phenol that is isolated or extracted from grapes, peanuts, berries, red wine, *etc*. RSV gets efficiently absorbed, but certain metabolite compounds take place due to its hasty metabolisms, such as sulfate derivative and glucuronide derivative, which aren't stable and subject to hasty urinary excretion 14, 15 [16]. One of the studies showed the constructive effects of RSV on the nigral region, revealed from a mouse PD model. There was also positive evidence of RSV providing a safeguard to the dopaminergic neurons. An RSV compound polydatin which is found as a prodrug is a natural glycosidic compound that is isolated from the rhizome of the plant *Polygonum cuspidatumis* found to modulate inflammation by decreasing the activation of NFκB and oxidative stress, thereby shielding the brain from any possible inflammatory impairment [15, 16, 17].

Hydroxytyrosol: The most important dietary source for hydroxytyrosol is mainly olive oil and olives (Olea European). These polyphenolic compounds are found to exert many protective actions against cardiovascular disorders and also type 2 DM. Studies conducted in several mouse models found that the hydroxytyrosol polyphenol can efficaciously cross the blood-brain barrier and exert an *in-vivo* neuroprotective activity. But due to its relatively poor bioavailability, it hasn't been proven efficient enough to incorporate for treatment purposes to date; investigatory studies are going on aiming to increase its bioavailability and decrease its rapid metabolism [7, 9, 11, 19].

Olive Oil: Natural products are structurally optimized by evolution to perform specific biological functions such as regulating endogenous defense mechanisms and interacting with other organisms. This property explains why they are important in infectious diseases and cancer. Polyphenols from extra virgin olive oil (EVOO), an important component of the Mediterranean diet, have recently piqued the interest of researchers. Extensive research has demonstrated that these bioactive molecules have potent therapeutic effects against various chronic diseases, including cardiovascular disease, diabetes, neurodegenerative disorders, and cancer.

Furthermore, the mechanisms of inhibition of oxidative stress-activated molecular signaling pathways by EVOO polyphenols are their potential roles in inflammation-mediated chronic disorders, including meta-analysis of population studies and clinical trials [19].

How Do These Polyphenol Agents Modulate the Cognitive Capabilities of Down syndrome Individuals: There is a rising curiosity about the potential of the natural polyphenol compounds for improving memory and learning and general cognitive capability reversing the age-related declinations. Nutritional supplementation to modulate the expression of certain genes and the signaling pathways to improve the functions of mitochondria can be a prominent stratagem to correct the clinically associated phenotypes that are linked to increasing the oxidative stress in DS patients and thereby can be very useful in reducing and delaying the pathological and clinical phenotypes allied with DS, thus refining the quality of life of the DS individuals [11, 13, 14, 18].

CONCLUSION: In this article, the focus was particularly on the polyphenol agents that act as a nutritional supplement in Down Syndrome patients for their multimodal activities in the altered metabolism pathways. Undeniably, the polyphenolic compounds network with the cellular metabolism, inducing the upkeep of energy balance through the modulation of NADPH, acetyl CoA, homocysteine metabolism, lipid oxidation, and oxidative DNA inhibition impairment.

Additionally, the polyphenol compounds can also modulate the signal transduction pathways regulating mitochondrial functions like respiration, mitochondrial-dependent cellular apoptosis, and oxidative phosphorylation. Polyphenols can also help regulate the ROS homeostasis and upregulate the transcription of antioxidant events, thus directly or indirectly affecting the neuronal viability, which is an essential parameter when taking the context of cognitive decline.

The cognitive phenotype in Down's syndrome is characterized by impairments in morphosyntax, verbal short-term memory, and explicit long-term memory. The anomalies occur mostly due to the extra pair of Chromosome 21.

Incorporating the recently surfaced biotechnological tools like CrisprCas9 in mouse models of Down syndrome that replicate the Trisomy 21 in humans is another novel approach on trend. Editing and limiting the chromosomal functionality or making changes at the onset of the embryonic genome may be a potent genetic engineering milestone.

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