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Study the Role of Antioxidants in the Controlling of Huntington's Disease

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ABSTRACT

Huntington's disease (HD) isa neurodegenerative disorderand generally related to a mutation in a gene**.** The mutation leads to the increasing in the triplet CAG repeating inside the coding section of the gene.Characteristics of Huntington's disease including the presence of 2 symptoms: abnormalities in the motor nerve cells and impairment of cognition.Nearly 9% of cases symptoms may begin earlier the age twenty years, in this case the disease identified as adolescent HD.The review aimed to study the huntingtons disease signs and symptoms, learning about causes and risks, Knowing the genetics of HD and types of antioxidant therapies used in HD. We concluded from the current review that HD is a disorder which has been stubborn to the treatment. In our review, we propose the using of antioxidants in the achievement of the disease state. Free radicals generation leading to the condition of oxidative stress (OS) destruction that causing loss of nerve cells in HD. Supplementation with antioxidants from natural source may cause reducing of oxidative stress that responsible for the pathophysiology of different dangerous illness for example,neurodegenerative illnesses. Oxygen Species mostly a free radical types that responsible for cells damaging and consequent death of cells because of the oxidization to sensitive constituents of cells that makes part of lipids, proteins, DNA, RNA. Glutamic acid is the main amino acid that preventing the neurodegeneration which responsible for HD people that are at great danger, as aged and newly detected patients.

KEYWORDS

HhuntingtonsDisease, Anti-oxidants, Neurodegenerative Illnesses.

Introduction

Huntington's disease (HD) is also called the Huntington's chorea which considered a neurodegenerative disease and mostly related to a mutation in a gene that responsible for a protein encoding called huntingtin (htt) (Dayalu and Albin, 2015). The mutation leads to the increasing in the triplet CAG repeating inside the coding section of the gene named IT15 that responsible for encoding of htt, and causinga sequence of multiple Q tract adjacentto the N-terminal of that protein.Characteristics of Huntington's disease including the presence of2main symptoms which are: abnormalities in the motor nerve cells and impairment of cognition (Ross and Tabrizi, 2011).A process of neurodegeneration is a very excited disease, while in the termof motor signs, it has a bi-phasic principle. It is also a basal ganglia disease. The initial stageof HDis described by actions that are involuntary and termed "chorea" (Roze *et al*.,2010; Rosas *et al*., 2008;Cowan andRaymond, 2006).Degeneration also occurs in this early stage in a type of neurons that called a cortical glutamatergic neuronswhich project to the striatum which explain the impairments in cognition and psychological disturbances that appearing in patients with HD (Walker, 2007).When the disease advanced and the death of neuronsincreased and furthermore affects additional striatal subpopulations,HD patients exhibit a symptoms similartoparkinson diseasesymptoms with bradykinesia and also rigidity episodes.In addition to the primary cause of neurons degeneration that occurs in this disease which is the toxic effect of the transformedhuntington protein, there is a furtherseveral methods, many of them are common to other disorders of neurodegeneration, i.e. misfolding of proteins, abnormalities in protein lysis, accumulation and deposition of proteins, unregulated transcriptional process, loss of mitochondrial functions,processes of oxidation,stimulationof glial cells alsothe events of local inflammation, all the above have also involved in the death of nerve cells of HD patients.In patients with HD signstypically start between thirtyto fifty years old but also maybegin at any age.HD may develops at theearly time in thesuccessional generation.Nearly 9% of cases symptoms may begin earlier the age twenty years, in this case the disease identifiedas adolescent HD, thatusuallyexisting with the symptoms of slow

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movement of Parkinson's disease rather than those of chorea (Stadtman, 2004).

HD still has no cure and patients may die in approximately ten to twentyyears after the diagnosis of disease (Factor and Friedman, 1997). There was some attempts with antiglutamatergic agents that used for reducingthe excitotoxicity effect within the damaged brain cellsdespite their efficacy was limited.During the latest years,different assemblies of novel complexes, as fatty acids that are unsaturated, Q10 co-enzyme, minocycline,inhibitors for histone deacetylases, have been restudied in preclinical models (Butler and Bates, 2006)

The process of oxidative tensionplays an important roles in the pathology of neuronal degenerative diseases asAlzheimer'sand Huntington's diseasesalso in parkinsons disease (Pohl *et al*.,2018; Christensen *et al*.,2009). Humans(CNS) is predominantlydelicate to thedamagingby oxidation due to its extraordinaryintakeof O_2 (nearlytwenty percent of whole body consumption of O_2) (Gaeta and Hider,2005). Many researchstated thatnumeroussamples related toneuronalbrain disease containslow concentrations of redox enzymes, superoxide dismutase, also the enzyme catalase. Additionally, reactive oxygen species (ROS) leading to the misfolding and proteins accumulation, and tothe oxidation of DNA or RNA (Desai *et al*.,2015; Chang *et al*.,2018). Oxidative stress also playing an important role in temporary ischemia of cerebrum,which is characterized by the disturbanceflow of blood, through this nextstage, O_2actions as substate of a successions oxidative reactions for many enzymes that leading to an increasing in oxidant species (Chan, 1996). Thus, the pharmacologic change of damaging by oxidation has beenplanned as a way for stroke medicines (Raza *et al.*,2011).All of these thoughts strongly boost the using of antioxidants by means of a probabletoolin the direction ofavoiding ROS role in the neuronal goals: numerous studies in the preclinical stageexplained the role of antioxidantsin reducing the oxidative tensionin addition to improvingthe impairments of cerebrum in patients with Alzheimer's disease.Several medicinesthat using in the treatment of Alzheimer's diseasebelonging to the antioxidantsproperties (Niedzielska *et al*.,2016).

The review aimed to:

1. Study the huntingtons disease signs and symptoms.
2. Learning about causes and risks of HD.
3. Knowing the genetics of HD.
4. Types of antioxidant therapies used in HD.

1- Symptoms of HD

The signs of HDare greatest commonly noticedat the agesbetweenthirty years tofifty years,while in other cases they mayalso initiate at every age (Jensen *et al*.,2018).In fifty percent of many cases, the symptoms that appear first in HD patients are the psychiatric symptoms.Their development is designated in the initial, middle, and delayed periods with a previous prodromal stage.Within the initial stages of disease, many hanges observed in subtle personality, physical abilitiesand cognition problems, irritability, and occurrence of temper swings, every one of them may beunobserved (Valeand Cardoso, 2015). Thesymptomsgenerally appear before the motorized symptoms (Arlington,2013).Virtuallyevery person suffering from HD finally exposed ananalogous physical signs, while the beginning, symptom development, and the mental and behavioral signsextension may differ significantly amongdifferent persons (Kremer, 2002; Wagle, 2000).

The most symptoms of HD are jerky, and randomly uncontrolledmovements. Many patients are not realized their involuntary movements (Dayalu and Albin, 2015).Chorea may be first exhibited as incomplete motions, loss of organization, andreduced saccadic opticalmovements (Walker, 2007). The common consequences involving corporeal variability, strange face expression, besidesa difficult speaking, mastication, and swallowing.disturbances in sleeping and loss of weight are also relatedsymptoms (Dickey andSpada, 2018).Swallowing difficulties causing loss of weightand subsequently may causemalnutrition (Aziz *et al*.,2008). HD of juvenile developed at a quicker rate combined with further declining in cognition, the slowly movement, tremors and rigidity, is more predominant in the juvenile HD (Dickey andSpada, 2018).

Cognitive ability isa progressiveimpairment and generally tend to decline and convertedto doting.Particularlythat affected are principle occupations, thatincluding a planning,suppleness in cognition, compendiousthought,statuteachievement, starting of properactivities, alsodamping of unsuitable actions (Montoya *et al*.,2006).With the progression of adisease, memory insufficienciesbegin to appear, including episodic deficits, procedural, andmemory of working.

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Described neuropsychiatric symptoms are depression, anxiety, reducing in displaying of emotions, egocentrism, dourness, and compulsive demeanor, the last one may causeaddictions, as well as alcoholism, baccarat, and extrasexuality(van Duijn,2007).Abstruseness in identification other people's – veexpressions are another observations.The presence of these indications is movableamong studies, with predictabledegrees for lifetime presence of psychologicalabnormalities amongthirty threeto seventy six percent. Recent behavioral changes in the results of HD including an increasing in suicide risks.Frequently, persons have lessattentiveness of chorea, emotional impairments and cognition (Murray *et al*.,2012).
Mutations in huntingtondisease are expressed through the patientsbody and linked withperipheral tissues abnormalities which caused by the expression exteriorof the brain. Theabnormalities are includingthe atrophy in muscles,failure of the heart, impairment intolerance to glucose,loosingof weight, osteoporosis, anddystrophy in testicles (van der Burg *et al*.,2009).

2 - Reasons and Risks

Defective gene identification in 1993 causes approximately all of HD.Huntington gene defect includesadditionalspecific code repeating in a unique small piecein chromosomenumber 4.Huntington normal gene includingseventeen to twenty of this code repetitions amongstthat oneentire of above 3,100 codes. This amiss which causingHDincludingfourty or extra repeats. Hereditary tests for HD are using for measurement the amount of repeats that occur in patients that havinga gene of huntington protein. Many scientists are excited to explain these mysteries in order to exist the solutionof Huntington's disease. These answersfurthermore may provide a significant insightsto theextensive range foradditionaldisorders associated with brain such as alzheimer's disease, Parkinson's and ALS or amyotrophic lateral sclerosis(Maiuri *et al*.,2017 ; Sturrock A, Leavitt, 2010).

3 - Genetics of HD

Every person has 2 replicas of huntingtin gene (HTT), that encodes for a type of protein calledhuntingtin protein abbreviated as (Htt). The other name of HTT is HD gene, also the gene IT15. Portion of that gene is a repetitivesegmentnamed a trinucleotide repeat expansion – a stubbyrepeat, thatdiffersamongpersons in length, alsocanmodifyits length amongst generations. These repeatsif existing in healthy genes, anactive mutation cansurge the repeatingamount and resulting in unreliable gene. If the size of the repeated segment reaching a definite threshold, itsproducts a differentformula of the protein, that called a mutant huntingtin protein (mHtt). Different functions of this proteinis the cause of many pathological variations, that in turn causing the symptoms of a disease. The mutation of HDis hereditarily dominant and fully penetrant; mutation in any of aindividual's HTT alleles causing that disease. The inheritance is not associated withsex, but through the distance of gene repeated section (Walker, 2007).

Genetic Mutation

The gene of HTTis positioned on the chromosomes 4short arm at 4p16.3. HTT containsa sequencingof DNA three bases which are: cytosine-adenine-guanine (CAG) that are frequentnumerous times, identified as a repeat of trinucleotide. CAG is a codonfor glutamine amino acid,thereforesuccessions of them resulting in the creation of a glutamine sequences identified as a polyglutamine tract,the frequentportion of the gene named the polyQ region (Katsuno*et al*., 2008).

Trinucleotide repeating classification, and resulting disease status, depending on the number of CAG repeating(Walker, 2007)

Count of repeats	**Classification**	**Status of the disease**	**Offspring risks**
Less than twenty- seven	Normal	not be affected	No risk
From twenty-seven to thirty-five	Intermediate	not be affected	Less than fifty percent
From thirty-six to thirty-nine	Reduced in Penetrance	Affected or not	fifty percent
More than fourty	Full in penetrance	affected	fifty percent

Usually, persons have less than thirty six frequent glutamines in the area of polyQ, producingthe huntingtin protein in the cytoplasm.Asequencing of thirty six or further glutaminescreating a protein withdifferent features.Thetransformedshape, namedthe mutant huntington (mHtt) which increasing the declinedegree of

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definitekinds of nerve cells. Areasinhuman brain having different quantities and depending on nerve cells types. Commonly, the amount of repeats of CAG is associated to how much of this processesarealtered, and accounts for approximatelysixty percent of thesedifferences of the age of the beginning of signs. Variationremaining is imputed to environmental factors and additional genes whichmodifying the mechanisms of HD.Nearlythirty six to thirty ninerecurrences resulting inreducing in the penetrance of the disease form, withabundant later beginning and slowering theprogression of signs. In certaincircumstances,onset may be so late, thesesigns are never observed.With a very great repeatingamounts (more than sixty), The beginning of HD can happenunder the age of twenty (juvenileHD). Juvenile HD is characterised by slowmovements, inflexibility, and shocks. This accounts for approximatelyseven percent of HD carriers (Squitieri *et al*.,2006; Nance andMyers, 2001).

Inheritance of HD

Huntington's diseases have an inheritance of autosomal dominant, which means thatindividual who is affected usuallyreceives one copy of the gene with an extendeda repeating of a trinucleotide from the parent that affected. Thenmutational penetrance is great, persons that having a copy of gene with mutation will exposing the huntingtons disease. In suchinheritance design, everyprogenyfrom affected personwill having about fifty percentdanger of receiving the allele that mutant, so is affected by the condition. This possibility is a sex-independent type (Passarge, 2001).

Repeating of a CAG trinucleotide numbering more than 28 are not stable through replication, and this condition of instability will increasing as the numeral repeats increased. Generallythis leading to different expansions with generations pass alternatively reproducing a strict copy for repeating the trinucleotide.Thecondition causing the numeral repeats to variation in sequential generations, like thisnon affected paternal with an "intermediary" repeats numbers between (twenty eight- thirty five), or " decreased penetrance" (thirty six- fourty), might pass in the copy of the gene that has an increasing in repeats numbers that producingwholly penetrant HD.Such increasing in the repeats number in sequential generations is identified as hereditary anticipation (Dayalu andAlbin, 2015).Variability is more in the process of spermatogenesis than oogenesises process;inherited alleles maternally are generally of a similar repeat size, while paternally inherited alleles have a greater chance of increasing in its length (Ridley *et al*., 1988).Infrequentlya new mutation may causing Huntington's disease, where neither parental has above thirty six repeats ofCAG (Semaka*et al*., 2006).

In a rare conditionswhere parents together having an prolongedgene of HD, the risk increasing to seventy five percent, when each parent has 2prolonged copies, the dangerwill increasing to one hundred percent (the whollyoffspring will suffering from HD). Personsthat having both affected genes are uncommon. Sometimes, HD considered the lone disease inwhich possession of a 2ndtransformed gene did not redound signs and development,howevermany scientists established that it can affect the phenotype and the level of progression (Squitieri *et al*., 2003).

4 - Therapies Related to Antioxidants Used for HD

Gathering of ROS within nerve cells, besidessuccessive oxidative stress, all of them are weakenedviascavengers for free radical thatclassifiedinto enzymatic andnon-enzymatic antioxidants. The first one (enzymatic)antioxidants considereda type of the defensive mechanisms of the body for destroying free radicals. The free radicals including superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (Gpx). Antioxidants of Non-enzymatic type areexemplified by retinoic acid, ascorbic acid (Vitamin C), glutathione (GSH), α-tocopherol (Vitamin E), flavonoids, carotenoids, and others. The beneficial approachthat experienced *in vitro* or in toxin or transgenic models of HD is given below:

Experiments that are Accomplished in Vitro Are

a. Catalytic antioxidants that containing metals, Metalloporphyrin,has developed as a novel category type of possibleremedial agents whichremove anextensive ranged reactive oxygen species. Another agent is a manganese porphyrin can bedescribedfor reducing death of cells in the in vitro model of HD (Browne*et al*., 1999).
b. Vitamin C or Ascorbic acid considered a strong antioxidant which may be gained exogenously, thatcausing the oxidization ofdehydroxyascorbic acid withthe existence of reactive oxygen species. Treatment of rodent

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cortical nerve cells in culture by glutamic acid causing a significant degeneration of nerve cells, which was totallysavedby co-treatmentwith ascorbic acid (Beal and Ferrante, 2004).

c. Vitamin E or α-tocopherol is also a strong antioxidant. Using a nerve cells-based assay, inducing of neuronal death by glutamic acid was significantly weakened in a dose-dependent mode by α-tocopherol. Idebenonetreatment in this in vitro model also resulted in whole protection of neurons in a dose-dependent manner (Stack *etal*.,2008).
d. Melatonin hormone, which acts as a good scavenger for hydroxyl, reactive nitrogen species, carbonate, and other radicals from organic group. Melatonin significantly decreaseddeoxy ribonucleic acid damaging and supports neurons survival (Albin *etal.*, 1992).
e. Selenium, is a necessarycomponentthat required by the enzyme glutathione peroxidase for the formation of active enzyme. Seleniumreduced the peroxidation of lipids and improvedthe morphologyof nerve cellsinside the ratsstriatum after treatment by quinolinic acid (Ferrante *et al*., 1985).
f. Creatine is a type of naturalcompounds that actsby means of antioxidants. Another function of creatine is bufferingthe intracellular energy reserves during its middle, phosphocreatine (PCr); also cause the stabilizing of intracellular calcium; and inhibiting the activation of transition pore within the mitochondria. Creatine supplements reduce the volume of striatal lesion produced bymalonate and the neurotoxins 3-NP
g. Tacrolimus or Fujimycin (FK-506) is a drug that consideredimmunosuppressive and mainly used for the loweringof allograft rejection. Newly, the role of FK-506 as neuroprotective effects were described in 3-NP model of HuntingtonsDisease.
h. Thepigments of carotenoid and phytochemical (Lycopene)is found in vegetables as well asfruits naturally, cause oxidative stress markers reduction and improvingthe behavior in a 3-NP induced rodent model of HD.

In the Models of HD Transgenic Mouse

a. Lipoic acid considered to be a critical cofactor to many types of enzymes andexistent as cofactor to pyruvic acid dehydrogenase enzyme and α -ketoglutaric acid dehydrogenase in mitochondria. It is considered an actual antioxidant whichused for the treatmentof impaired energy metabolism associated disease. It also plays an important role in the inducing the Nrf-2/ARE pathway. Supplementation by lipoic acid in diet causinganincreasingin survival, as well aslateloss of weight in N171-82Q transgenic rats. Pyruvic acid is important in glycolysis, and has the properties of antioxidants (Ferrante *et al*., 1987).
b. BN82451 is a brain-penetrable that has the effect of neuroprotection, including the lipid peroxidation inhibition. R6/2 mice that administerof BN82451 resulted in an extension of survival, significant motor function improvements, with gross morphology improvements, as well asa number of ubiquitin positive aggregates in R6/2 micewas significant decreased when compared with control mice that untreated.
c. Creatine presentwithin cellsin the form of free creatine, also in the form ofphosphocreatine (PCr), these compounds together forming the whole creatine pool. Withinhigher energy requirements tissues inbrain and striated muscles, phosphocreatine doing a buffer action through which the phosphorylation of adenosine diphosphate (DAP) to adenosine triphosphate (ATP) occurs. The process ofphosphor group transferring is accomplished by creatine kinase (CK). Supplementation with creatine in R6/2 and the N171-82Q transgenic mouse improving the motor performance, extended survival, the loss inthe body massas well as the brain weight attenuation besides neuronal atrophy reduction.
d. Four-N-trimethylammonium-3-hydroxy-butyric acid (L-carnitine) which playing an importantaction in mitochondrial acyl-coenzyme A/ratio of coenzyme A controlling, fatty acids oxidation by peroxisomes, or may acting as a scavenger for free-radical. It is active in plasma membrane damage preventionthat triggered by the action of reactive oxygen species. Administration excess of L-carnitine by the N171-82Q transgenic mice causethe extendin surviving, ameliorate motor performance, and also cause the intranuclear aggregatesamount decreasing.
e. Treatment with phenolic extract from grape seed in the models of fly and R6/2 mouseof HD cause extend in life extent, and reducemotor deficits in the R6/2 mice.
f. Artificial triterpenoids thatequivalentsto 2-Cyano-3,12- Dioxooleana-1,9-Dien-28-Oic acid (CDDO), are of excessiveattention because they haveproperties as anti-inflammatory and antioxidants. Triterpenoids conserved the striatal volumes of the N171-82Q mice, by stopping the degeneration of the middle spiny nerve cells (White *et al*.,1997; Johri and Beal, 2012).

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Conclusion

HD is a disorder from a neurodegenerative typeand has been stubborn to the treatment. Even though the numerous researchdwelled on the disease, no benefit treatmentsconsidered to assuages the signs of HD have been advanced. This might be related to the nature complexityof this disease and to the absence of evidences on a detailed molecular goalto the therapeutic interference. We are knowing that oxygen considered an importantparticle for surviving of living organisms over the world besideswithin the body. Oxidative stress condition typicallyharmful to the body andhappensas soon as there is an additionalgeneration of free radicals or decreasing in the levels of antioxidant within the body. Therefore,this review suggests using of antioxidants in theachievement ofthe diseasestate. Free radicals generation leading to the condition of oxidative stress (OS) destructionthat causing loss of nerve cellsin HD. Supplementation with antioxidants from natural source may cause reducing of oxidative stress that responsible for the pathophysiology of differentdangerousillnessfor example,neurodegenerative illnesses. Oxygen Species mostly a free radical typesthat responsible for cells damaging and consequentdeath of cells because of the oxidizationto sensitive constituentsof cells that makes part of lipids, proteins, DNA, RNA. Glutamic acid is the main amino acid that preventingthe neurodegeneration which responsible for HD people that are at greatdanger,as aged and newly detected patients. The neurogenesis process in adults considered an important tool for the treatment of HD brains,and it is contributing to the adult brain functions. Many types of antioxidants regulate the process of neurogenesis. Natural antioxidants may provide proneurogenicas wells as neurotropic, neuroprotectionand supportingto the brain of HD patients.

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