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Mitochondrial Dysfunction in Autistic Children and Oral Coenzyme Q10 Supplementation Treatment

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Abstract

This review was conducted in order to determine the effect of Oral Coenzyme Q10 supplement on children diagnosed with Autism spectrum of disorders. Among the most common treatments used for autistic spectrum disorders, vitamin/mineral supplements are considered to be the most common treatments. An oral vitamin/mineral supplementation has benefits in improving the nutritional and metabolic status of children with ASD; these include the improvement of oxidative stress, inflammation, but research on using these supplements for treating Coenzyme Q10 supplement on autistic children has been limited. Mitochondrial dysfunctions occur in a subset of ASD. Different cases usually occur due to genetic anomalies or mitochondrial respiratory pathway abnormalities. In addition, they have also been associated with different behaviours in children. There have been many studies that reveal evidence of mitochondrial dysfunction (MtD) in children with ASD. Various drugs of either synthetic or natural origin applied in the treatment of brain disorders need to cross the BBB before they can be used in Alzheimer's disease, Parkinson's disease, autism, and many other chronic illnesses. This review suggests that a Coenzyme Q10 supplement is a reasonable MtD therapy to consider for most children diagnosed with Autism.

Keywords: Autism spectrum of disorders; Children; Mitochondrial dysfunction; Coenzyme Q10

Introduction

Psychiatry disorders can have a threat on the society's health [1,2]. Autism spectrums of disorders (ASD) are considered neurodevelopmental disorders. In psychiatry, autism is characterized by ADI-R. Children who are affected by this disease usually suffer from impaired social interactions, speech disabilities, repetitive and/or compulsive behaviours, deficits in memory, learning, or other neurological functions, hyper-or hypo sensitivity to sensory stimuli, anxiety, and difficulty to adapt to new environments/habits [3]. Epidemiological studies has presented that the prevalence of ASD has increased in recent years. Due to the poor understanding of this disease, there has been no biomarkers identified as characteristic of autistic spectrum disorders and there is no certain treatment approach [4]. In the etiology of autism, several disturbances in biochemical and inflammatory factors have been observed. The etiology of ASD have been seen from genetic, neurological and environmental factors, like oxidative stress, and its clinical implications in ASD is now of particular interest [4,5]. Recent studies have shown alterations in immuno-inflammatory autistic individual's system. High levels of post-mortem individuals with autism revealed high levels of tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin 1-beta (IL-1-β) in addition studies conducted on brain tissue and cerebrospinal fluid [6,7].

Mitochondrial dysfunction (MtD) is likely precipitated by oxidative stress and inflammatory response, and could contribute to a number of diagnostic symptoms and comorbidities of ASD (abnormal energy metabolism, chronic gastrointestinal problems, and abnormalities in fatty acid oxidation). It was thought one day that MtDs is rare, but today they are regarded as one of the most common metabolic disorders, stress oxidative and inflammation response in children [8]. Classical mitochondrial dysfunctions occur in a subset of ASD cases and are usually caused by genetic anomalies or mitochondrial respiratory pathway abnormalities [9]. In addition, they have also been associated with behavioural problems in children Evidence of mitochondrial dysfunction (MtD) in children with ASD is revealed by many studies [10]. It is, however, associated with laboratory evidence of lowered mitochondrial functioning. MtD may be considered active macrophages and monocytes response, and are substantial with respect to their active role in metabolic functions and immune-inflammatory system [11]. In pathophysiology of many children with ASD such as Asperger Syndrom, Autistic disorder, the role of stress oxidative, immuno-inflammatory system impairments, and inflammatory have been presented [12]. Due to the extraordinary dependence of synaptic transmission on high energy output from, neurodegenerative and epilepsy may occur in children with MtD and immuno-inflammatory, [13]. This may be a result from the fact that the aerobic metabolic demand of the brain is very high, making it extraordinarily vulnerable to any decline in mitochondrial efficiency increased levels of MCP-1 in neurons inflammation [14].

Coenzyme Q10 (CoQ10) is considered as an effective endogenously synthesized-lipid soluble antioxidant, acting to either prevent stress oxidative and inflammatory, by regenerating vitamin E or by interacting with superoxide or other reactive oxygen species [15]. CoQ10 is a key component of the oxidative phosphorylation process in the mitochondria [16]. Apart from its anti-oxidative function, CoQ10 appears to modulate immune functions by unknown mechanisms [17].

Furthermore, this review will also present evidence that inflammation and stress oxidative of ASD is controlled by a coenzyme Q supplementation in children with ASD.

Mitochondrial Dysfuction (MtD) in Autistic Children

In 1959, the first disorder of mitochondrial function was described by Luft [18]. On the other hand, the true incidence and prevalence of mitochondrial disorders and dysfunction remain unclear [19]. The nervous system is the most commonly affected system in mitochondrial disorders [20]. The most of MtD of children present with neurologic signs and patients demonstrate intellectual dysfunction or psychiatric disturbances [21]. If the recognition of mitochondrial disorders in children is considered challenging, their diagnosis in childhood is even more challenging [22]. Lactic acidosis is considered the most recognized laboratory abnormality in patients with mitochondrial disorders. A Dysfunction in the electron transport chain causes a decrease in the production of adenosine triphosphate. When lactic acidosis is present, consideration must be given to the fact that it is not specific to mitochondrial dysfunction. Elevated serum levels of lactate can be seen with neurodegenerative diseases, seizures and metabolic disorders [23]. During the initial evaluation, investigations for autistic disorders that may mimic mitochondrial disorders should be undertaken. The electron transport chain is part of a complex energy generating system inside cells [24]. An overall decrease in mitochondrial functions may result from defects in other systems. Plasma amino acids, urine amino and organic acids, pyruvate and acylcarnitine profiles are usually included in metabolic studies [25]. Elevations of protein, lactate, pyruvate and even white blood cells were demonstrated in the cerebrospinal fluid of patients with mitochondrial dysfunctions and autistic children [26]. In addition, MtD and oxidative stress may explain the high boy to girl ratio found in autism due to increased boy's vulnerability to these dysfunctions. Mitochondrial dysfunction's Biomarkers have been identified, but they seem widely under-utilized despite the available therapeutic interventions [27].

Potential Treatments of MtD in Autistc Children; Antioxidant and Anti-inflammatory Compounds

The more adept clinicians become at recognizing mitochondrial dysfunction in ASD, the more opportunities there will be for improving and ultimately treating the diagnosis. The severity of symptoms might differ, it is essential that most symptoms have to be addressed as soon as possible [28]. Some of the most important behavioral and social treatment approached for ASD [29].

Nutritional supplementations are given to improve reduced oxidative stress and inflammatory along with factors to improve decreased ER stress and mitochondrial ROS in autistic children [30]. Once effective treatment for MtD is implemented, the underlying pathophysiology and autistic symptoms in affected individuals would be expected to either improve or cease worsening [31]. Moreover, potentially effective drugs and vitamins/supplements are used most often in the treatment of ASD children [32]. In recent studies using anti-oxidant compounds showed a significant improvement in social interaction and communication using the Aberrant Behavior Checklist (ABC) scale of patients with ASD. Some antioxidants used in patients found no difference on the total ABC, but instead a significant improvement on the clinical laboratories [33]. In many of the randomized, placebo-controlled studies, the dose of antioxidant compounds added to nutrition autism had an effect on total ABC, but decreased the irritability subscale [34]. Recently, studies have reported that patient with ASD and who are treated with anti-inflammatory compounds showed the most improvement in social interaction and communication and decreased serum TNF-α and IL-6 levels [35,36]. These results indicate that subgroups of children with ASD, who are most amenable to treatment with anti-inflammatory compounds, may be identified by objective inflammation. This study recently showed that anti-inflammatory compounds have a better bioavailability [37]. Therefore, it could be developed for the treatment of ASD. By inhibiting cyclooxygenase-1 (COX-1), various plant compounds can have anti-inflammatory activities [38]. The local increase in oxidative is resulted from the accumulation of COX-1 enzyme in microglia in ASD patients. The use of immuno-modulatory treatments has been considered for children diagnosed with ASD [39]. These compounds are shown to mimic brain-derived neurotrophic factors (BDNF) and inhibit microglial activation and proliferation, which reduced symptoms in focal brain inflammation [40].

Moreover, they improved memory in ASD and inhibited autism-like behavior [14,37,41,42]. Unfortunately, there are few clinically approved anti-inflammatory drugs that can be used in children with ASD.

Coenzyme Q10 Supplementation Treatment; Reduced Oxidative Stress and Inflammation

Coenzyme Q10 (CoQ10) and reduced nicotinamide adenine dinucleotide (NADH) are common antioxidant supplements that effect the central nervous system (CNS), which have been used for several decades as dietary supplements for general health maintenance. The major form of CoQ10 is the reduced form ubiquinol (Qx), which is responsible for its antioxidant properties. CoQ10 increases the cellular ATP production via mitochondrial oxidative phosphorylation, and their supplementation could help improve fatigue and other symptoms in CFS [43].The potential anti-inflammatory effect of CoQ10 or its reduced form has been suggested through in vitro and in vivo studies [44]. For instance, Q10 was able to decrease the inflammatory score based on the mRNA level of TNF-α-, interleukine-6, C reactive protein, STAMP2 and NADPH oxidase [45-47]. Coenzyme Q is required for Voltage Dependent Anion Channel (VDAC) ferricyanide reductase activity as proposed. The requirements required for coenzyme Q for the function of a pore protein, such as VDAC, is not without precedence; for example, binding of coenzyme Q to the UCP in the mitochondria is required for optimal function [48].

Several studies have shown that there is the MtD which reduces the rate of ATP synthesis and is the central agent of energy production in most CFS Autism spectrum disorders [23,49,50]. For its part, CoQ10 supplementation has been evaluated in many illnesses [51-53], such as with chronic diseases [54], but few studies have been published neuropsychiatric conditions and fibromyalgia.

CoQ10 is a naturally occurring flavonoid with potent antioxidant, anti-inflammatory properties that are found in green plants, herbs, and seeds [44]. Autism Spectrum Disorders are characterized by protein aggregates and inflammation as well as oxidative stress in the central nervous system (CNS) [55]. Multiple biological processes are linked to ASD such as depletion or insufficient synthesis of neurotransmitters, oxidative stress, and abnormal mitochondrial function. Furthermore, damaging of the blood brain barrier (BBB) in the CNS can also lead to various ASD children [56].

The inflammation markers were shown to increase in the brain of many ASD patients including IL-1β and TNF-α, molecules secreted from mast cells, as well as MCP-1 and IL-8, which are chemotactic for Mast Cells. In particular, plasma levels of IL-8 and IL-6 were increased in children with ASD. IL-6 and TNFα- could disrupt the BBB and cause "focal encephalitis" in specific brain areas, thus contributing to the pathogenesis of ASD [57]. Anti-oxidant supplementation, which is a therapeutic strategy in treating this neurological disorder, could have positive clinical benefits [58]. The various drugs of either synthetic or natural origin applied in the treatment of brain disorders need to cross the BBB before they can be used on patients diagnosed with Alzheimer's disease [59], Parkinson's disease [60], autism [61] and many other chronic illnesses [62]. Even though synthetic drugs are used for the management of neurodegenerative disorders, they still have many side effects CoQ10 are seen to have promising therapeutic agents because many dietary supplements have anti-inflammatory, antioxidative, as well as anticholinesterase activities. It has been suggested that these molecules may modulate the autonomic function by regulating the synthesis of endogenous catecholamines and acetylcholine [63]. Many researchers have been inclined towards natural compounds, which may have benefits and have minimal side effects.

Dietary Sources of Coenzyme Q10

All organisms, including humans, can synthesize ubiquinones. Foods such as rapeseed (canola), fish, meats, oils and sesame are good nutritional sources of CoQ 10, while lower levels can be originated in most fruits, dairy foods, cereals and vegetables [64]. Levels over 50 mg/kg may be found in beef, pork, and chicken liver and heart. Also, oils of vegetable are completely rich in CoQ10. Grape, Broccoli and cauliflower are diffident bases of CoQ10. Most berries and fruit signify a poor-to-very-poor source of CoQ10, excluding avocado, that has a comparatively elevated CoQ10 [65].

Dietary Sources of Antioxidants

Anti-oxidant supplementation is a therapeutic strategy in treating neurological disorders. This supplementation is such as herbs rich in polyphenols. Among these plants are *Heracleum persicum* and *Ziziphus jujuba* [66], fennel (*Foeniculum vulgare*) [67], celery (*Apium graveolens*) [68-70] that have antioxidant properties.

Conclusion

However, today the etiology of ASD is poorly understood. Potential mechanisms that may link MtD to neuronal dysfunction, clinical symptoms, pathogenesis of autism include stress oxidative, immune and inflammatory response. MtD can be diagnosed via certain biomarkers and is potentially treatable. Therefore, increased efforts of MtD screening of all individuals affected with autism should be encouraged. The purpose of this systematic review was to provide a mechanism of the therapeutic intervention strategies, like Co-Q10 supplementation, in treating ASD children with MtD, could have positive clinical benefits. In the future, oral Co-Q10 supplementation could be used as a promising therapeutic treatment for ASD children, due to their anti-inflammatory and antioxidative, as well as their anticholinesterase activities.

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References

1. Afrishama R, Aberomand M, SoliemaniFar O, Kooti W, Ashtary-Larky D, et al. (2016) Levels of salivary immunoglobulin A under psychological stress and its relationship with rumination and five personality traits in medical students. The European Journal of Psychiatry 30: 41-53.
2. Afrisham R, Sadegh-Nejadi S, SoliemaniFar O, Abromand M, Kooti W, et al. (2015) Evaluating the salivary alpha-amylase level under psychological stress and its relationship with rumination and the five personality traits. Journal of Mazandaran University of Medical Sciences 25: 22-33.
3. Fernell E, Gillberg C (2010) Autism spectrum disorder diagnoses in Stockholm pre-schoolers. Research in developmental disabilities 31: 680-685.
4. Chakrabarti S, Fombonne E (2005) Pervasive developmental disorders in preschool children: Confirmation of high prevalence. Am J Psychiatry 162: 1133-1141.
5. Abrahams BS, Geschwind DH (2008) Advances in autism genetics: on the threshold of a new neurobiology. Nat Rev Genet 9: 341-355.
6. Onore C, Careaga M, Ashwood P (2012) The role of immune dysfunction in the pathophysiology of autism. Brain Behav Immun 26: 383-392.
7. Li X, Chauhan A, Sheikh AM, Patil S, Chauhan V, et al. (2009) Elevated immune response in the brain of autistic patients. J Neuroimmunol 207: 111-116.
8. Chauhan A, Gu F, Chauhan V (2015) Mitochondrial dysfunction in autism. studies on psychiatric disorders. Springer 355-372.
9. Hadjixenofontos A, Schmidt MA, Whitehead PL, Konidari I, Hedges DJ, et al. (2013) Evaluating mitochondrial DNA variation in autism spectrum disorders. Ann Hum Genet 77: 9-21.
10. Rossignol DA, Frye RE (2012) Mitochondrial dysfunction in autism spectrum disorders: A systematic review and meta-analysis. Mol Psychiatry 17: 290-314.
11. Illi J, Miaskowski C, Cooper B, Levine JD, Dunn L, et al. (2012) Association between pro-and anti-inflammatory cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance and depression. Cytokine 58: 437-447.
12. Doong SH (2013) Associations between pro-and anti-inflammatory cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance and depression in patients prior to surgery for breast cancer. University of California, San Francisco.
13. Rasool M, Malik A, Qureshi MS, Manan A, Pushparaj PN, et al. (2014) Recent updates in the treatment of neurodegenerative disorders using natural compounds. Evidence-Based Complementary and Alternative Medicine.
14. Theoharides TC, Asadi S, Patel AB (2013) Focal brain inflammation and autism. J Neuroinflammation 10: 46.
15. Crane FL (2001) Biochemical functions of coenzyme Q10. J Am Coll Nutr 20: 591-598.
16. Matthews RT, Yang L, Browne S, Baik M, Beal MF (1998) Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects. Proceedings of the National Academy of Sciences 95: 8892-8897.
17. Sobreira C, Hirano M, Shanske S, Keller RK, Haller RG, et al. (1997) Mitochondrial encephalomyopathy with coenzyme Q10 deficiency. Neurology 48: 1238-1243.
18. Ernster L, Ikkos D, Luft R (1959) Enzymic activities of human skeletal muscle mitochondria: A tool in clinical metabolic research. Nature 184: 1851-1854.
19. Thorburn DR (2004) Mitochondrial disorders: prevalence, myths and advances. J Inherit Metab Dis 27: 349-362.

20. DiMauro S, Schon EA (2008) Mitochondrial disorders in the nervous system. Annu Rev Neurosci 31: 91-123.
21. Koenig MK (2008) Presentation and diagnosis of mitochondrial disorders in children. Pediatr Neurol 38: 305-313.
22. Michelson D, Shevell M, Sherr E, Moeschler J, Gropman A, Ashwal S (2011) Evidence report: Genetic and metabolic testing on children with global developmental delay report of the quality standards subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 77: 1629-1635.
23. Lin MT, Beal MF (2006) Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature 443: 787-795.
24. Oliveira G, Diogo L, Grazina M, Garcia P, Ataide A, et al. (2005) Mitochondrial dysfunction in autism spectrum disorders: A population-based study. Developmental Medicine and Child Neurology 47:185-189.
25. Regenold WT, Phatak P, Marano CM, Sassan A, Conley RR, et al. (2009) Elevated cerebrospinal fluid lactate concentrations in patients with bipolar disorder and schizophrenia: Implications for the mitochondrial dysfunction hypothesis. Biological psychiatry 65: 489-494.
26. Zecavati N, Spence SJ (2009) Neurometabolic disorders and dysfunction in autism spectrum disorders. Current Neurology and Neuroscience Reports 9: 129-136.
27. Poling JS, Frye RE, Shoffner J, Zimmerman AW (2006) Developmental regression and mitochondrial dysfunction in a child with autism. Journal of Child Neurology. 21: 170-172.
28. Rossignol DA, Bradstreet JJ (2008) Evidence of mitochondrial dysfunction in autism and implications for treatment. American Journal of Biochemistry and Biotechnology 4: 208-217.
29. Kumar B, Prakash A, Sewal RK, Medhi B, Modi M (2012) Drug therapy in autism: A present and future perspective. Pharmacol Rep 64: 1291-1304.
30. Adams JB, Holloway C (2004) Pilot study of a moderate dose multivitamin/mineral supplement for children with autistic spectrum disorder. Journal of Alternative and Complementary Medicine 10: 1033-1039.
31. James SJ, Cutler P, Melnyk S, Jernigan S, Janak L, et al. (2004) Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. The American Journal of Clinical Nutrition 80: 1611-1617.
32. Rimland B, Callaway E, Dreyfus P (1978) The effect of high doses of vitamin B6 on autistic children: a double-blind crossover study. Am J Psychiatry 135: 472-475.
33. Castejon A, Spaw J (2014) Autism and oxidative stress interventions: Impact on autistic behavior. Austin J Pharmacol Ther 2: 6.
34. Hardan AY, Fung LK, Libove RA, Obukhanych TV, Nair S, et al. (2012) A randomized controlled pilot trial of oral N-acetylcysteine in children with autism. Biol Psychiatry 71: 956-961.
35. Boris M, Kaiser CC, Goldblatt A, Elice MW, Edelson SM, et al. (2007) Effect of pioglitazone treatment on behavioral symptoms in autistic children. J Neuroinflammation 4: 3.
36. Chez MG, Dowling T, Patel PB, Khanna P, Kominsky M (2007) Elevation of tumor necrosis factor-alpha in cerebrospinal fluid of autistic children. Pediatr Neurol 36: 361-365.
37. Cohly HH, Panja A (2005) Immunological findings in autism. Int Rev Neurobiol 71: 317-341.
38. Cryer B, Feldman M (1998) Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used non-steroidal anti-inflammatory drugs. Am J Med 104: 413-421.
39. Muller N (2002) Use of cox-2 inhibitors for the treatment of schizophrenia, delusional disorders, affective disorders, autism or tic disorders. Google Patents.
40. Monje ML, Toda H, Palmer TD (2003) Inflammatory blockade restores adult hippocampal neurogenesis. Science 302: 1760-1765.
41. Theoharides TC, Angelidou A, Alysandratos K-D, Zhang B, Asadi S, et al. (2012) Mast cell activation and autism. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease 1822: 3441.
42. Theoharides TC, Asadi S, Panagiotidou S, Weng Z (2013) The missing link in autoimmunity and autism: Extracellular mitochondrial components secreted from activated live mast cells. Autoimmunity reviews 12: 1136-1142.
43. Maes M, Mihaylova I, Kubera M, Uytterhoeven M, Vrydags N, et al. (2008) Coenzyme Q10 deficiency in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is related to fatigue, autonomic and neurocognitive symptoms and is another risk factor explaining the early mortality in ME/CFS due to cardiovascular disorder. Neuro endocrinology letters 30: 470-476.
44. Faust K, Gehrke S, Yang Y, Yang L, Beal MF, et al. (2009) Neuroprotective effects of compounds with antioxidant and anti-inflammatory properties in a Drosophila model of Parkinson's disease. BMC Neurosci 10: 109.
45. Carmona MC, Lefebvre P, Lefebvre B, Galinier A, Benani A, et al. (2009) Co-administration of coenzyme Q prevents rosiglitazone-induced adipogenesis in ob/ob mice. Int J Obes (Lond) 33: 204-211.
46. Neyrinck AM, Catry E, Sohet FM, Cani PD, Pachikian BD, et al. (2015) Lack of anti-inflammatory effect of coenzyme Q10 supplementation in the liver of rodents after lipopolysaccharide challenge. Clinical Nutrition Experimental 1: 10-18.
47. Tsai KL, Chen LH, Chiou SH, Chiou GY, Chen YC, et al. (2011) Coenzyme Q10 suppresses oxLDL induced endothelial oxidative injuries by the modulation of LOX-1-mediated ROS generation via the AMPK/PKC/NADPH oxidase signaling pathway. Molecular Nutrition and Food Research 55: S227-S240.
48. Naoi M, Maruyama W, Yi H, Akao Y, Yamaoka Y, et al. (2007) Neuroprotection by propargylamines in Parkinson's disease: Intracellular mechanism underlying the anti-apoptotic function and search for clinical markers. Neuropsychiatric Disorders An Integrative Approach: Springer 121-31.
49. Bosetti F, Brizzi F, Barogi S, Mancuso M, Siciliano G, et al. (2002) Cytochrome c oxidase and mitochondrial F1F0-ATPase (ATP synthase) activities in platelets and brain from patients with Alzheimer's disease. Neurobiol Aging 23: 371-376.
50. Palmieri L, Persico AM (2010) Mitochondrial dysfunction in autism spectrum disorders: Cause or effect? Biochim Biophys Acta 1797: 1130-1137.
51. Hershey AD, Powers SW, Vockell AL, Lecates SL, Ellinor PL, et al. (2007) Coenzyme Q10 deficiency and response to supplementation in pediatric and adolescent migraine. Headache 47: 73-80.
52. Overvad K, Diamant B, Holm L, Holmer G, Mortensen SA, et al. (1999) Coenzyme Q10 in health and disease. Eur J Clin Nutr 53: 764-770.
53. Sarter B (2002) Coenzyme Q10 and cardiovascular disease: A review. J Cardiovasc Nurs 16: 9-20.
54. Tran MT, Mitchell TM, Kennedy DT, Giles JT (2001) Role of coenzyme Q10 in chronic heart failure, angina and hypertension. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 21: 797-806.
55. Herbert MR (2010) Contributions of the environment and environmentally vulnerable physiology to autism spectrum disorders. Curr Opin Neurol 23: 103-110.
56. Theoharides TC, Zhang B (2011) Neuro-inflammation, blood-brain barrier, seizures and autism. J Neuroinflammation 8: 168.
57. Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA (2005) Neuroglial activation and neuroinflammation in the brain of patients with autism. Ann Neurol 57: 67-81.
58. Kerr DS (2010) Treatment of mitochondrial electron transport chain disorders: A review of clinical trials over the past decade. Molecular genetics and metabolism. 99: 246-255.
59. Orhan G, Orhan I, Subutay-Oztekin N, Ak F, Sener B (2009) Contemporary anticholinesterase pharmaceuticals of natural origin and their synthetic analogues for the treatment of Alzheimer's disease. Recent Patents on CNS Drug Discovery. 4: 43-51.
60. Tetrud JW, Langston JW (1989) The effect of deprenyl (selegiline) on the natural history of Parkinson's disease. Science 245: 519-522.

61. Carocho M, Ferreira IC (2013) A review on antioxidants, pro-oxidants and related controversy: natural and synthetic compounds, screening and analysis methodologies and future perspectives. Food and Chemical Toxicology 51: 15-25.
62. Haddad PS, Azar GA, Groom S, Boivin M (2005) Natural health products, modulation of immune function and prevention of chronic diseases. Evidence-Based Complementary and Alternative Medicine 2: 513-520.
63. Majumdar A, Nirwane A, Kamble R (2014) New evidences of neurotoxicity of aroclor 1254 in mice brain: potential of coenzyme q10 in abating the detrimental outcomes. Environ Health Toxicol 29: e2014001.
64. Fantuzzi M, Udell RG (2007) Solubilized CoQ-10 and carnitine. Google Patents.
65. Pravst I, Zmitek K, Zmitek J (2010) Coenzyme Q10 contents in foods and fortification strategies. Crit Rev Food Sci Nutr 50: 269-280.
66. Afrisham R, Aberomand M, Ghaffari MA, Siahpoosh A, Jamalan M (2015) Inhibitory effect of *Heracleum persicum* and *Ziziphus jujuba* on activity of alpha-amylase. Journal of Botany 824683.
67. Mansouri E, Kooti W, Bazvand M, Boroon MG, Amirzargar A, et al. (2015) the effect of hydro-alcoholic extract of *Foeniculum vulgare* mill on leukocytes and hematological tests in male rats. Jundishapur Journal of Natural Pharmaceutical Products 10.
68. Kooti W, Ghasemiboroon M, Asadi-Samani M, Ahangarpoor A, Abadi MNA, et al. (2014) The effects of hydro-alcoholic extract of celery on lipid profile of rats fed a high fat diet. Advances in Environmental Biology 325-331.
69. Kooti W, Mansouri E, Ghasemiboroon M, Harizi M, Ashtary-Larky D, et al. (2014) The Effects of hydroalcoholic extract of *Apium graveolens* leaf on the number of sexual cells and testicular structure in rat. Jundishapur Journal of Natural Pharmaceutical Products 9.
70. Kooti W, Ghasemi-boroon M, Ghafourian M, Asadi-Samani M, Harizi M, et al. (2015) The effects of celery leave extract on male hormones in rats. Journal of Herb Med Pharmacology 4.