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Mini Review

Lepidium Sativum Seeds as a Suggested Complex Nutritional Supplement to Treat Biomarkers Related Deficits in Autism

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Abstract

Autism as a neurodevelopmental disorder is characterized by persistent autistic features such as impaired social communication, restricted and repetitive behavior, and intellectual disabilities. As a disorder, autism has several ubiquitous co-morbidities, among which is sleep disorders, epilepsy, attention deficit, and hyperactivity. No effective treatment for the core symptoms of autism is available until now. There is increasing interest in natural products, especially pharmaceutical plants as mono-therapy for the treatment of the core symptoms and co-morbidities of autism. In this review we discuss the safety and effectiveness of *Lepidium sativum* seeds as treatment strategy for the early intervention in autism. Up to our understanding of the etiological mechanisms of autism such as oxidative stress, impaired gut microbiota, abnormal lipid metabolism, neuroinflammation, and glutamate excitotoxicity and based on the biomarkers repeatedly recorded to confirm the contribution of these pathways in autism, *L. sativum* can be suggested as monotherapy. Being an excellent source of non-starch carbohydrates, omega-3 polyunsaturated fatty acids and their precursors, flavonoids, and vitamin E, *L. sativum* can be suggested as complex supplement to ameliorate the symptoms of autism. Although it is very interesting to find the effectiveness of this plant in treating autism however, convincing pre-clinical data showing efficacy and safety in treating autism is mandatory.

Keywords: Autism; Biomarkers; Lepidium sativum; Oxidative stress; Gut microbiota; Neuroinflammation; Glutamate excitotoxicity

Introduction

Autism as one of the most common neurodevelopmental disorders is characterized by deficits in social communication, repetitive and restricted behaviors, with multiple sensory abnormalities. Autism is dramatically increasing in prevalence and is now considered an epidemic. There are no objective means to diagnose autism. Diagnosis is made objectively, based on the apparent behavior of the individual [1]. A biomarker is "a distinguishing variable that is accurately measured and assessed as a sign of normal biological manners, pathogenic status, or pharmacological responses to treatment strategy." They decrease our dependence on patients, caregivers, or clinician scores and are principally important for individuals who are unable to describe their physical or mental problems such as children with autism. Studies of autism biomarkers can enhance our ability to predict abnormal development early in infancy and hence can proceed through early intervention that might be of great help because till now effective medical treatments for the core symptoms of the disorder are still lacking. There is great evidence about the alteration of amino acids, hormones, metabolites and other biomarkers in autistic individuals compared to age- and sex-matched controls. These abnormalities can be observed in the gastrointestinal, immunologic, neurologic and toxicological systems of the body. In addition, there are unifying etiological mechanisms such as increased susceptibility to oxidative stress, immune dysfunction, glutamatergic dysfunction, and abnormal lipid metabolism. The variances of the biomarkers from the standard present the chance to create a panel of biomarkers that when selectively developed could result in an objective early diagnosis with direct correlation with the severity of autism for everyone [2-8].

Lepidium sativum

In the search for a natural supplement that can ameliorate most of the abnormalities described above as autistic phenotypes, *Lepidium sativum,* also known as Garden cress was on the top of the list. *L. sativum* is an edible plant belonging to the family of mustard. Seeds, leaves and roots of *L. sativum* are of therapeutic potency; but the plant is mostly cultured for seeds in order to get mucilage for various reasons (Figure 1). In Europe and America, the leaves are used in salad [9]. Seeds have reported the presence of flavonoids, coumarins, sulphur glycosides, triterpenes, sterols and various imidazole alkaloids [10]. The major components of this alkaloid fraction are lepidine and semi-lepidine as shown in Figure 2. A rare

group of imidazole alkaloid [9]. The major secondary compounds of this plant are glucosinolate contents [11]. There are red, yellow and black varieties of *L. sativum* up to their seed color [12]. Additionally, seeds contain 25% of protein, 14-24% of lipids, 33-54% of carbohydrates and 8% of crude fiber [13,14]. The carbohydrates of the *L. sativum* seeds comprise of 90.0% non-starch polysaccharides and 10% of starch. The seed bran has high dietary fiber content and also it has a high-water holding capacity (74.3%). *L. sativum* seed contains 20-25% yellowish oil with high percentage of alpha linolenic acid (32-34.0%) [15]. It also has high quantity of polyunsaturated fatty acids (PUFA) (46.8%) and monounsaturated fatty acids (MUFA) (37.6%) and also contains natural antioxidants such as tocopherols and carotenoids which protect the oil from rancidity. Seven imidazole alkaloids in which five lepidine B,C,D,E, and F (dimeric) and two new monomeric alkaloids namely semilepidinoside A and B; and sinapic acid and sinapine were reported in seeds of *L. sativum* [9,16]. Benzyl isothiocyanate and benzyl cyanide are main volatile constituents of seed. Whereas, β-sitosterol and α-tocopherol are unsaponifiable matter of *L. sativum* seeds. It also contains mucilages, which upon hydrolysis gives arabinose, galactose, glucose, mannose, xylose and various ironic acids that are the most frequently observed components.

Figure 1: Lepidium sativum, leaves, flowers, and seeds.

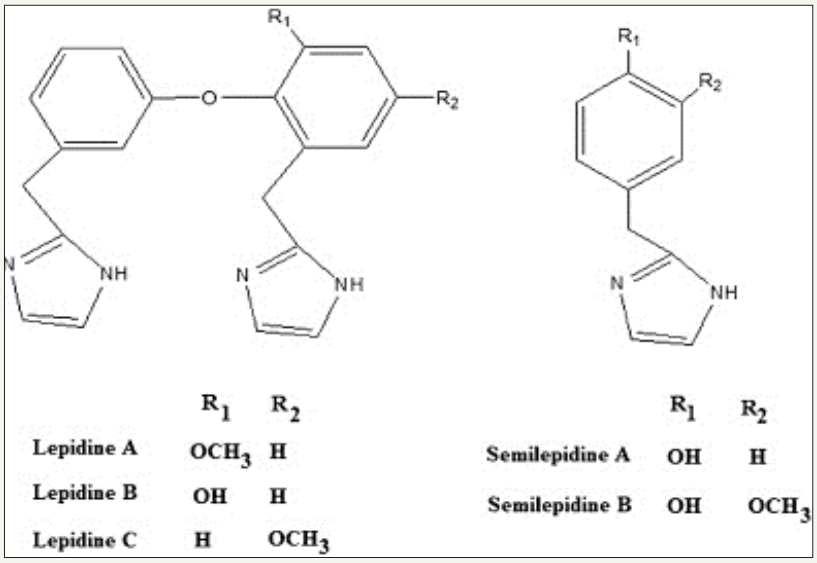

Figure 2: Structures of lepidine and semi lepidine as major components of L. sativum seeds.

Lepidium sativum as suggested supplement to treat autism

Up to our understanding of the etiological mechanisms of autism, now let us discuss the reasons behind our choice of this plant as recommended supplement to treat this disorder. First, based on the fact that p-cresol levels are significantly higher in blood, urine, and feces of individuals with autism compared to neurotypical children, and it negatively affect the homeostasis of their colonic epithelial cells through the induction of DNA damage [17,18] the 90.0% of non-starch polysaccharides in *L. sativum* can greatly help in the decrease of p-cresol as deleterious compound. Nutritional intervention studies [19] show that the amount of resistant starch or non-starch carbohydrates in the diet is inversely proportional to the amount of p-cresol in feces and urine. Based on this *L. sativum* can correct the impaired gut microbiota as confirmed etiological mechanism in autism. It is well documented that while harmful Clostridium species were observed abundant in feces of children with autism, another type of beneficial bacteria,

Bifidobacterium, was reduced [20-25]. In the recent work of [26] non-starch carbohydrates (e.g. Fructans, Galactooligosaccharides and Hemicellulose) were suggested as additives to induce the growth of Bifidobacterium in order to mimic breast-fed infant-like microbiota in a formula-fed product. These types of non-starch polysaccharides have been shown to increase the abundance of beneficial bacteria, such as *bifidobacteria* and *lactobacilli*, while decreasing counts of potential pathogens, such as *Clostridium* and *Escherichia coli*. This can support the use of *L. sativum* which is rich with non-starch carbohydrates to treat autism.

Second, it is well known that diets rich in ω-6 PUFA are known to have an effect on immune response, as their derivatives such as prostaglandins and leukotrienes are pro-inflammatory. Interestingly, patients with autism have a higher detected ratio of ω-6 PUFA/ω-3 PUFA compared to healthy control [27]. Immune dysfunction which is often defined in children with autism as well as their family members [28] is frequently related to diets rich in ω-6 PUFA leading to a significantly higher ω-6 PUFA/ ω-3 PUFA as autistic phenotype. [29] reported that individuals with a high ω-6/ ω-3 ratio diet were found to be more vulnerable to the psychological and immunological impact of stress than those with a more balanced ω-6/ω-3 ratio. The ratio of fatty acids namely linoleic acid (LA) and alpha linolenic acid (ALA) as precursors of ω-6 and ω-3 respectively in the diet plays an important role in enrichment of ALA in tissues and further conversion to ω-3 PUFAs (EPA, and DHA). Being one of the richest sources of omega-3 fatty acid and contains 29-34.5% of ALA, *L. sativum* can be suggested to increase brain EPA and DHA and correct the imbalance of ω-6 PUFA/ ω-3 PUFA ratio repeatedly recorded as marker of autism [30,31].

Flavonoids are polyphenolic compounds that are commonly present in plants and have biological effects on animal cells [32]. Plants containing these bioactive compounds have been used of their favorable effects on human health, decreasing inflammation, stimulating cognition and avoiding cancer [33-36]. Glutamate-mediated excitotoxicity as autistic phenotype is a major factor in neuronal loss. Notably, there is evidence that estrogens are neuroprotective, but their therapeutic use in humans is limited by the increased risk of cancer. Here, we provide evidence that the flavonoid in plants acts as a modulator of estrogen receptors to promote the generation of neurons in vitro and protects against glutamate-mediated neurotoxicity as effectively as the synthetic estrogen estradiol [37]. Moreover, [33-36] highlight the evidence for the potential role of plant flavonoids to inhibit neuroinflammation through an attenuation of microglial activation and associated cytokine release, iNOS expression, nitric oxide production and NADPH oxidase activity. Moreover, they indicate that flavonoid mode of action in the regulation of immune events appear to be mediated by their actions on intracellular signaling pathways, including the nuclear factor-κB (NF-κB) cascade and mitogen-activated protein kinase (MAPK) pathway. As such, flavonoids represent important precursor molecules in the journey to develop of a new generation of drugs capable of lessening neuroinflammation and neurodegenerative disease. Based on our knowledge about the contribution of glutamate excitotoxicity, oxidative stress, NF-κB, and MAPK signaling as etiological mechanisms in autism, and in relation to the flavonoid availability as component of *L. sativum*, the seed of this plant can be of great help to ameliorate the clinical presentation of all these etiological mechanisms usually appear as social interaction impairment, repetitive behavior, anxiety, epileptic seizures, and hyperactivity.

Children with autism often have diets that are relatively deficient in many nutrients, including vitamin E [38]. The use of vitamin E in autism is mostly driven by its antioxidant properties in amending the effects of reactive oxygen species (ROS) or mitochondrial dysfunction as one of the most prevalent metabolic disorders in autism [39,40]. Oxidative damage to proteins has been documented in the brain and other tissues in individuals with autism. Some of the signs that demonstrate the occurrence of abnormal redox metabolism and/or mitochondrial dysfunction in individual with autism are the presence of chronic pain, increased fatigue on the day following infrequent effort, dysautonomia, and severe gastrointestinal disease [41]. Up to this, *L. sativum* which is rich with vitamin E can be suggested as supplement to ameliorate oxidative stress and mitochondrial dysfunction in individuals with autism.

Conclusion

Up to our knowledge on the pathological mechanisms of autism, our recorded biomarkers presenting the contributed pathways, and our awareness with the medicinal properties and the ingredients *of L. sativum*, it can be suggested as mono-therapy to ameliorate the core symptoms of autism and the concomitant co-morbidities. Of course, pre-clinical data is highly recommended.

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