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Review Article

The Role of Antioxidants in the Management of Obsessive-Compulsive Disorder

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Obsessive-compulsive disorder (OCD) is a chronic neuropsychiatric disorder that has a significant effect on the quality of life. The most effective treatment for OCD is the combination of selective serotonin reuptake inhibitors (SSRI) with cognitive behavior therapy (CBT). However, several adverse effects have been linked with this usual pharmacotherapy, and it is unsuccessful in many patients. The exact pathophysiology of OCD is not completely known, though the role of oxidative stress in its pathogenesis has been proposed recently. This review presents an overview of animal and human studies of antioxidant treatment for OCD. The use of antioxidants against oxidative stress is a novel treatment for several neurodegenerative and neuropsychiatric disorders. Among antioxidants, NAC was one of the most studied drugs on OCD, and it showed a significant improvement in OCD symptoms. Thus, antioxidants could be promising as an adjuvant treatment for OCD. However, a limited number of human studies are conducted on these agents, and for better judgment, human studies with a large sample size are necessary.

1. Introduction

Estimates indicate that 1–3% of the population are affected by obsessive-compulsive disorder (OCD) as a chronic neuropsychiatric disease, which severely harms the quality of life [1]. Hoarding, skin picking (excoriation), and hair-pulling disorder (trichotillomania) formerly known as OCD; nevertheless, in the Diagnostic and Statistical Manual of Mental Disorders-version 5 (DSM-5), they are in the obsessive-compulsive-related disorders (OCRD) section (Figures 1) [2]. The risk factors of OCD are environmental factors, impaired neurotransmissions, autoimmune processes, genetic factors, infections, and stressors or trauma-driven incidents [3–8]. The most well-known pathophysiology of OCD is anomalies of the central nervous system (CNS), particularly in the serotonin, dopamine, and glutamate pathways [9, 10]. According to clinical guidelines [11], the first line of OCD treatment is cognitive behavior therapy and exposure and response prevention (CBT/ERP) or one selective serotonin reuptake inhibitor (SSRI) or a combination of one SSRI with CBT/ERP. So far, the superiority of either of these three types of treatment has not been proven. OCD symptoms are manageable using a variety of approaches, such as switching to a different SSRI or clomipramine, increasing SSRI dose, or augmenting with an atypical neuroleptic drug, such as risperidone and aripiprazole [11]. Anxiety, insomnia, nausea, diarrhea, constipation, dizziness, sedation, and sexual dysfunction are complications of SSRIs at higher dosages [12]. Although the existing therapeutic methods are highly efficient, the treatment cannot be initiated or completed in many

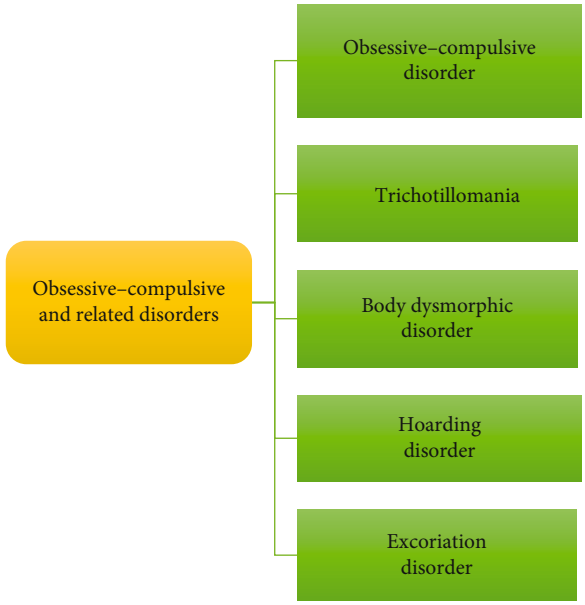

Figure 1: Obsessive-compulsive and related disorders. Based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

OCD patients; furthermore, a number of patients are resistant to these therapeutic managements [13, 14].

So far, the exact pathophysiology and etiology of OCD remain unknown; however, besides neurotransmitter imbalance, oxidative stress could somewhat imply the pathophysiology of OCD. Oxidative stress is caused by the lack of balance between the generation of oxidative free radicals and neutralizing antioxidants [15]. Free radicals are defined as reactive nitrogen species (RNS) or reactive oxygen species (ROS), with a shortened half-life. Some mechanisms, such as ischemia, lipid peroxidation, and trauma, can produce free radicals [16]. Oxidative stress can severely damage the brain due to these reasons: (1) moderate antioxidant defenses, (2) redox-catalytic metals, (3) high percentage of phospholipids, and (4) high oxygen utilization [17]. Oxidative stress in the brain can cause harmful damages, including neuroinflammation, mitochondrial dysfunction, inhibition of neurogenesis, impaired neurotransmission, acceleration of aging and apoptosis, impaired neuroplasticity, and dysfunctional neuronal integrity (Figure 2) [18]. In particular, basal ganglia have vulnerability to injury by free radicals because of high concentrations of catecholamines in this area. Abnormal neurotransmission at the dopaminergic nerve cell endings may arise due to injuries to cells throughout the catecholamine metabolic process through free radicals [19, 20]. A higher association of the existence of free radicals in comorbidity of OCD and major depressive disorder (MDD) was reported in a study. Even so, there is an apparent relationship between pure OCD and the antioxidant enzyme deficits [21]. Recent studies have shown more activity of free radical metabolism and the weakness of antioxidant defense system in OCD. By increasing free radicals, cell membranes become less permeable through disrupted structures of phospholipids as the pivotal constituent of cell membranes. Significant elevations occur in malondialdehyde (MDA) concentrations due to lipid peroxidation in OCD patients. In addition, a significant decrease is observed in the level of nonenzymatic antioxidant vitamin E, which is associated with an increase in MDA levels. Serotonin levels decreased in the brain, in the coupling sites, by a direct effect of MDA (Figure 3) [22, 23]. The antioxidant system does not adequately buffer systemic oxidative imbalance in OCD patients. Stress markers significantly increased in OCD patients, and this could increase cellular injury by oxidizing DNA and lipids. A systematic review revealed elevated levels of 8-hydroxideoxiguanosine (8-OHdG), MDA, glutathione peroxidase (GSH-Px), and superoxide dismutase (SOD) but diminished concentrations of total antioxidant status (TAS), vitamin C, and vitamin E (Vit. E) in OCD patients. DNA damage and an increase in lipid peroxidation are the main types of oxidative-stimulated cellular injury between patients with OCD [24]. In a case-control study, patients with new OCD diagnosis were observed following a 12-week treatment with fluoxetine. At the same time, significant decreases and increases were reported in the oxidative stress indicator in serum, Thiobarbituric Acid Reacting Substances (TBARS), and the antioxidant parameter plasma (ascorbate), respectively. They also found that elevated lipid peroxidation was accompanied by an antioxidant balance impairment in OCD patients [25]. Since there is evidence of the potential function of oxidative stress in neurodegenerative diseases, e.g., OCD, antioxidant therapy should be examined in OCD patients. Antioxidants suppress the chain reaction of oxidative stress and prevent damage to cell constituents [26]. Antioxidants have to be provided only via dietary supplementation, as biologic systems are not able to manufacture them by nature. Here, we reviewed literature data on the treatment of OCD with the antioxidants.

2. Methods

The electronic database PubMed, Embase, and Scopus were searched using the following keywords from commencement to August 2020 for animal studies and clinical trials relevant to antioxidants and management of OCD. The searched keywords were obsessive-compulsive disorder, obsessive-compulsive related disorder, OCD, OCRD, trichotillomania, hoarding, excoriation, nail-biting, oxidative stress, antioxidants, lipid peroxidation, DNA damage, marble-burying behavior, N-acetyl cysteine, *Crocus sativus*, *Benincasa hispida*, *Cannabis sativa*, *Hypericum perforatum*, *Citrus aurantium*, *Colocasia esculenta*, *Curcuma longa*, *Tabernaemontana divaricata*, *Lagenaria siceraria*, *Withania somnifera*, Minocycline, L-carnosine, *Echium amoenum*, *Silybum marianum*, and *Valeriana officinalis*. Inclusion criteria were clinical trial or animal study on the use of antioxidants in OCD, and full texts accessible on-line in English, with no limits of publishing date. Exclusion criteria were duplicated published materials and review articles. Data were collected between April 2020 and August 2020 (Figure 4).

3. Results

3.1. Overview. Finally, results comprised 11 and 15 investigations on animal and human studies, respectively, and four

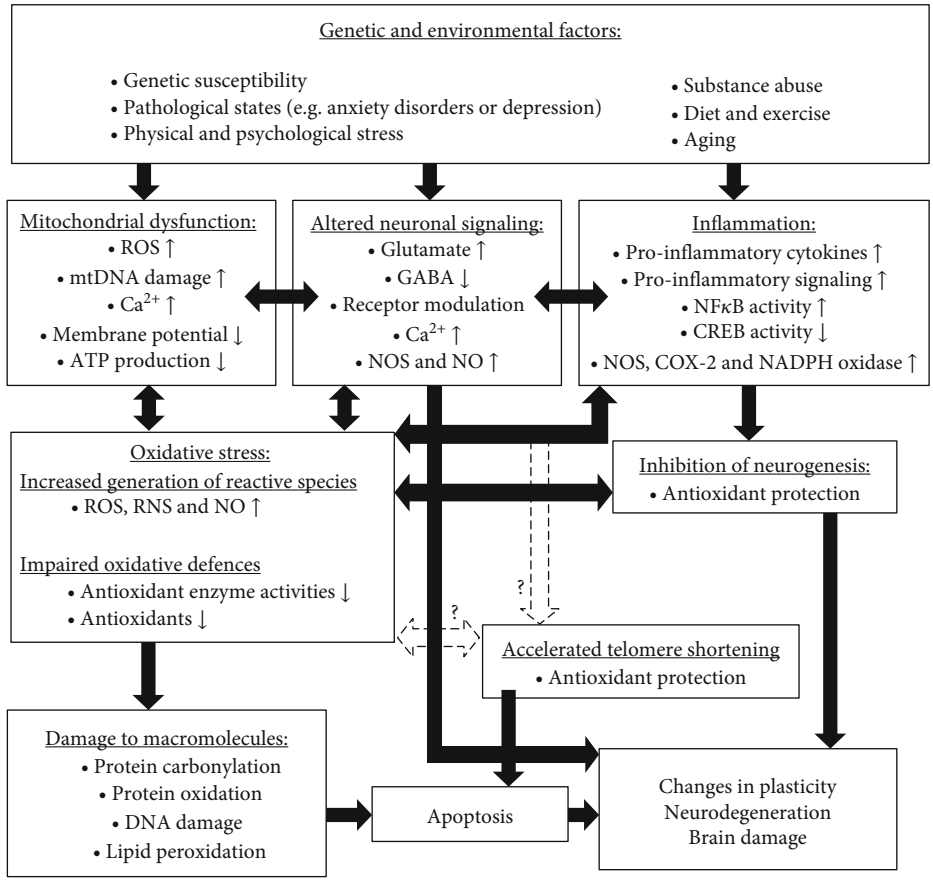

Figure 2: Hypothetical mechanisms of oxidative stress-induced neuronal damage. Abbreviations: COX-2: cyclooxygenase 2; CREB: cAMP response element-binding; GABA: γ-aminobutyric acid; NADPH: nicotinamide adenine dinucleotide phosphate; NFB: nuclear factor B; NO: nitric oxide; NOS: nitric oxide synthase; RNS: reactive nitrogen species; ROS: reactive oxygen species. Reproduced with permission from [15].

systematic reviews. Tables 1 and 2 summarize these studies. Among 11 animal studies, nine studies utilized the marble-burying model to evaluate obsessive and compulsive behaviors. This model has a good reputation for animals for the assessment of compulsive-like behaviors, which requires no behavioral trainings or pharmacologic manipulations [27]. mCPP (the nonselective serotonin receptor agonist, m-chlorophenylpiperazine) was used in a trial to induce excessive self-grooming in an animal model [28]. Excessive grooming behaviors in animals are considered to have similarity to the symptoms of OCD and trichotillomania [29]. Grooming behaviors include vibration, face and head washing, body grooming, scratching, paw licking, head shaking, and genital grooming [30]. In another research, compulsive behavior is stimulated by quinpirole. Duration and frequency of stops, occurrence of ritualistic behaviors, and number of visits to other objects were behavioral measures in this study [31]. This model is produced by chronic therapy of rats with quinpirole (a dopamine (D2/D3) agonist) two times a week for 5 weeks [32]. All of the clinical trials reviewed in this study used the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) for assessing the OCD severity. This scale has 10 items for examining OCD, including the time expended on obsession/-compulsions, interference and distress from obsession/compulsions, resistance, and control over the obsessions and compulsions [33].

3.2. Animal Studies

3.2.1. N-Acetyl Cysteine (NAC). NAC is an antioxidant that has been used as an antidote for paracetamol overdose. NAC is the cysteine precursor, which is utilized as a substrate to glutathione (GSH). GSH is one of the main endogenous antioxidant molecules in the brain that protects cells from oxidative stress. The therapeutic efficacy of NAC is related to its capacity to regulating both biosynthesis of GSH and cystine–glutamate antiporter activity [34, 35]. Egashira et al. investigated the effect of NAC on marble-burying test. Male mice grouped into 5 clusters each receiving the following drugs, respectively: Fluvoxamine (30 mg/kg, PO), Mirtazapine (3 mg/kg, IP), NAC (150 mg/kg, IP), α-tocopherol (10, 30, and 100 mg/kg, PO), and Fluvoxamine (10 mg/kg) with NAC (100 mg/kg). A significant reduction was observed in the marble-burying behavior scores by the effect of NAC. Moreover, Fluvoxamine and Mirtazapine significantly suppressed the marble-burying behavior. Combination of Fluvoxamine and NAC had no additional effects on mice. However, the antioxidant, vitamin E, did not change the

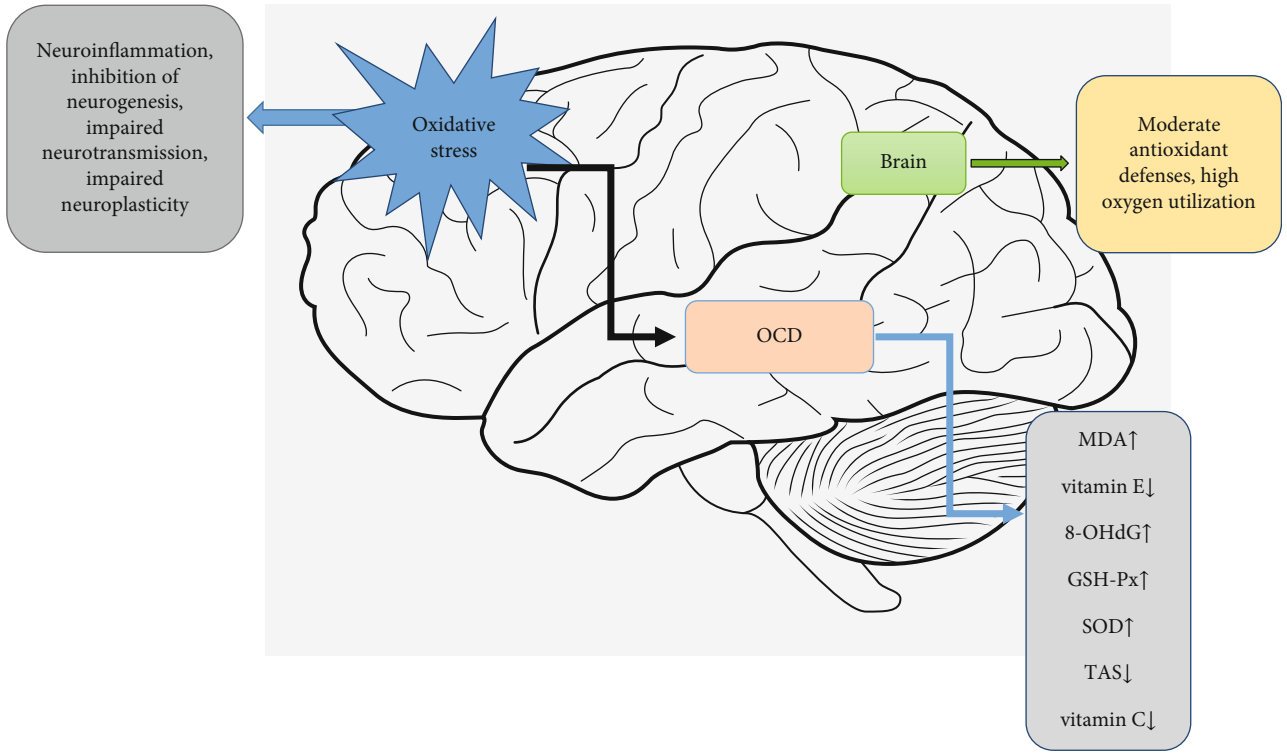

Figure 3: Role of oxidative stress in the pathophysiology of OCD. Abbreviations: MDA: malondialdehyde; 8-OHdG: 8-hydroxideoxiguanosine; GSH-Px: glutathione peroxidase; SOD: superoxide dismutase; TAS: total antioxidant status.

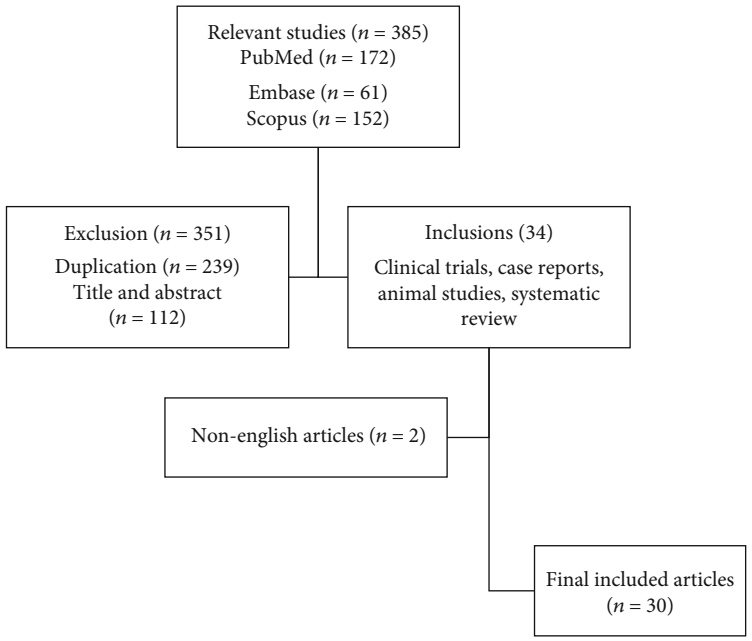

Figure 4: Flow diagram of study selection.

number of marbles burying behavior, which suggested that the anti-OCD impact of the NAC may not be because of its antioxidative properties and the glutamatergic system has a major contribution to the marble-burying behavior. In all the groups mentioned above, total locomotor activity did not change significantly throughout the marble-burying behavior. Results demonstrated that decreased numbers of marbles buried by mice cured with NAC could be expressive of an anti-OCD property [36].

3.2.2. Crocus sativus (Saffron). Crocus sativus from the Iridaceae family is known for its neuromodulatory properties.

Table 1: Antioxidant drugs for obsessive-compulsive and related disorders: animal studies.

Drug	Study	Animal	Dose (mg/kg) and duration	Model	Result	Year
N-acetyl cysteine	Egashira et al. [36]	Male mice	Acute treatment: 150 and Fluvoxamine (30)	Marble-burying model	Inhibit of marble-burying behavior ($P < 0.05$)	2012
Crocus sativus	Georgiadou et al. [28]	Male Wistar rats	Acute treatment: 30, 50	mCPP induced OCD-like behavior	Significant decrease in number and duration of grooming ($P < 0.05$)	2012
Benincasa hispida	Girdhar et al. [41]	Male Swiss albino mice	Acute treatment: 200, 400, 600 and fluoxetine (5, 10, 15)	Marble-burying model	Significant decrease in number of marble-burying behavior of extract+fluoxetine group ($P < 0.001$)	2010
Cannabis sativa	Casarotto et al. [45]	Male mice	Acute treatment: 15, 30, 60 chronic treatment: 30 for 7 days	Marble-burying model	Significant decrease in number of marble-burying activity ($P \leq 0.05$)	2010
Hypericum perforatum	Skalisz et al. [50]	Male Swiss albino mice	Acute treatment: 150, 300 chronic treatment: 300 for 21 days	Marble-burying model	Significant decrease in number of marble-burying activity in acute treatment ($P < 0.02$) chronic treatment: ineffective ($P > 0.10$)	2004
Citrus aurantium	Pultrini et al. [53]	Male Swiss mice	Acute treatment: 500,1000 chronic treatment: 500, 1000 for 15 days	Marble-burying model	Significant decrease in number of buried marbles in both groups ($P \leq 0.05$)	2006
Colocasia esculenta	Kalariya et al. [56]	Male Swiss albino mice	Acute treatment: 25, 50 and Fluoxetine (5).	Marble-burying model	Significant decrease in number of buried marbles ($P \leq 0.05$)	2015
Curcuma longa	Chimakurthy and Murthy [31]	Male Wistar rats	Chronic treatment: 5, 10 for 35 days	Quinpirole induced obsessive-compulsive model	Significant decrease in repetitive cleansing and grooming, and frequency of stops at objects ($P < 0.05$)	2010
Tabernaemontana divaricata	Chanchal et al. [68]	Male Swiss albino mice	Acute treatment:100, 200, 300 and fluoxetine (5, 10, 20)	Marble-burying model	Significant decrease in number of marble-burying behavior ($P < 0.0001$)	2015
Lagenaria siceraria	Prajapati et al. [71]	Male Swiss albino mice	Acute treatment: 25, 50 and fluoxetine 10.	Marble-burying model	Significant decrease in number of marble-burying behavior ($P < 0.001$)	2011
Withania somnifera	Kaurav et al. [73]	Swiss albino mice	Acute treatment: MEWS = 50, AEWS = 10, 25, 50, 100, and fluoxetine (5, 10, 15)	Marble-burying model	Significant decrease in number of buried marbles: AEWS ($P < 0.001$) and MEWS ($P < 0.0001$)	2012

Abbreviation: OCD: obsessive-compulsive disorders; mCPP: m-chlorophenylpiperazine; MEWS: methanolic extract of Withania somnifera; AEWS: aqueous extracts of Withania somnifera.

Crocin is the major water-soluble active ingredient of saffron. In terms of the structure, crocin belongs to the carotenoids, with a reputable potential antioxidant activity. Carotenoids have a polyene skeleton consisting of double bond conjugates in their molecular structure being involved in their potent antioxidant activities [37]. Crocin acts as an exclusive and strong antioxidant in neurons [38]. An animal study evaluated the therapeutical potentiality of crocin in an animal model of compulsive behavior. In this study, Georgiadou et al. examined the capability of crocin to antagonize mCPP stimulated excessive self-grooming in male Wistar rats. After random grouping of rats into six clusters, individual groups were treated with the following drugs: NaCl+NaCl; NaCl +crocins 30 mg/kg; NaCl+crocins 50 mg/kg; mCPP 0.6 mg/kg+NaCl; mCPP 0.6 mg/kg+crocins 30 mg/kg; and mCPP 0.6 mg/kg+crocins 50 mg/kg. The grooming activity of rats treated with mCPP and crocins was greater than that observed in their control match. Eventually, crocin reduced mCPP-stimulated excessive self-grooming in rats without affecting the motor activity. These observations are

Table 2: Antioxidant drugs for obsessive-compulsive and related disorders: clinical studies.

Drug	Study	Study design	Dose (daily)	Clinical outcome	Number of patients	Year
N-acetyl cysteine	Oliver et al. [74]	SR	2400-3000 mg	Reduce the severity of symptoms	206	2015
	Minarini et al. [76]	SR	600-3000 mg	Promising results were found in trials for treatment of excoriation	421	2016
	Smith et al. [75]	SR	800-2400 mg	Results remain inconclusive	162	2016
	Ooi et al. [77]	SR	2000-2400 mg	Improvement in OCD symptoms.	The studies listed above +74	2018
	Barroso et al. [78]	Case report (6 months)	1200-1800 mg	Complete regrowth of hair	1	2017
	Kiliç and Keleş [79]	Case report (3, 2 months, 3 weeks)	1200 mg	Complete cure in symptoms	3	2019
Minocycline	Esalatmanesh et al. [82]	12 weeks RDBPCT	200 mg	Significant improvement in OCD symptoms ($P = 0.003$)	102	2016
	Rodriguez et al. [81]	12 weeks open-label	200 mg	No significant improvement in Y-BOCS ($P = 0.90$) improve symptoms in early-onset OCD	9	2009
L-carnosine	Arabzadeh et al. [85]	12 weeks RDBPCT	1000 mg	Significant decrease in Y-BOCS score ($P < 0.001$)	44	2017
EPA	Fux et al. [89]	12 weeks preliminary cross-over PCT	2000 mg (+SSRIs)	No significant different between placebo and EPA ($P = 0.001$)	11	2004
Folic acid	Tural et al. [91]	12 weeks RDBPCT	5 mg (+40 mg fluoxetine)	No significant improvement in Y-BOCS ($P = 0.400$)	36	2019
Crocus sativus	Esalatmanesh et a. [94]	10 weeks DBCT	30 mg (±100 mg fluvoxamine)	Safe and effective as fluvoxamine ($P = 0.47$)	50	2017
Echium amoenum	Sayyah et al. [99]	6 weeks RDBPCT	500 mg	Significant decrease in Y-BOCS ($P = .035$)	44	2009
Silybum marianum	Sayyah et al. [107]	8 weeks RDBCT	600 mg (+30 mg fluoxetine)	Significant decrease in Y-BOCS ($P = 0.0001$)	35	2010
	Grant and Odlaug [108]	Case report (6, 8, 4 weeks)	300 mg	Improvement in OCD symptoms	3	2015
Valeriana officinalis	Pakseresht et al. [112]	8 weeks RDBPCT	765 mg	Significant improvement in OCD symptoms ($P < 0.0001$)	31	2011
Hypericum perforatum	Taylor & Kobak [92]	12 weeks open-label trial	900 mg	Significant improvement in Y-BOCS ($P = 0.001$)	12	2000
	Kobak et al. [93]	12 weeks RDBPCT	600-1800 mg	No significant improvement in Y-BOCS ($P = 899$)	60	2005
Withania somnifera	Jahanbakhsh et al. [114]	6 weeks RDBPCT	120 mg (±SSRI)	Significant decrease in Y-BOCS ($P < 0.001$)	30	2016

Abbreviation: OCD: Obsessive-Compulsive Disorders; NAC: N-acetyl cysteine; TS: Tourette syndrome; TTM: trichotillomania; SR: systematic review; CGI: Clinical Global Impression Scale; RDBPCT: randomized, double-blind, placebo-controlled trial; SSRI: selective serotonin reuptake inhibitor; Y-BOCS: Yale-Brown Obsessive-Compulsive Scale; PCT: placebo-controlled trial; NIMH-TSS: National Institute of Mental Health Trichotillomania Symptom Severity.

suggestive of possible alleviation of the mCPP-stimulated excessive self-grooming by crocin through an antagonistic activity at the 5-HT2C receptor site [28].

3.2.3. Benincasa hispida (Kundur). Benincasa hispida from the Cucurbitaceae family is endemic to the Asian tropical regions. *B. hispida* fruit has wide uses to treat nervous illnesses [39]. Antioxidant activity of *B. hispida* was reviewed in a study; seed extract, aqueous and methanolic extracts of dried ripe peels, skin, pulp, and seed of wax gourd extracts showed a significant free radical scavenging potential [40]. The influence of methanolic extract of *B. hispida* (MEBH) fruit was investigated in an animal study by Girdhar et al. They used the marble-burying model to evaluate compulsive activities on male Swiss albino mice. Six groups of mice received the following drugs in IP administration: 200, 400,

600 mg/kg of MEBH or 5, 10, 15 mg/kg of fluoxetine or 200 mg/kg of MEBH and 5 mg/kg of fluoxetine. The control group received NaCl (10 mL/kg, IP). To find out the implication of the serotonin path ways in OCD, they performed pretreatment administering of 300 mg/kg of p-chlorophenyl alanine (PCPA), a serotonin depleting agent, for three consecutive days and 24 h, followed by 600 mg/kg of MEBH or 15 mg/kg of fluoxetine. Results show that 400 and 600 mg/kg of MEBH dose-dependently exhibited considerable anticompulsive effect, and it was comparable to 10 and 15 mg/kg of fluoxetine. Also, coadministration of MEBH and fluoxetine significantly reduced marble-burying behavior. Overall locomotor action did not change significantly throughout the marble-burying behavior. On the other hand, mice pretreated with PCPA showed a partial but significant reduction in the inhibitive impact of MEBH, whereas they reported complete elimination of the burying behavior by fluoxetine. MEBH, therefore, significantly exhibits an anticompulsive impact on marble-burying test in mice, which is possibly attributable to an enhancement in serotonergic function [41].

3.2.4. Cannabis sativa (Marijuana). Cannabis sativa from the Cannabaceae family has wide uses in folk medicine. Recent studies have indicated that Cannabidiol (CBD), the nonpsychotomimetic component of Marijuana, has potential antioxidant activities, such as modulation of nitric oxide synthase expression and protection of cellular structures from ROS damage. CBD can affect the redox balance by modification of both oxidant and antioxidant activities. By interrupting free radical chain reactions, CBD captures free radicals or transforms them into types with lower activity [42–44]. The antioxidative activities of CBD are suggestive of a therapeutical usage as neuroprotecting agents. An animal study by Casarotto et al. examined the efficacy of CBD on male mice in the marble-burying behavior. The study included four experiments. (1) To investigate CBD impacts in the marble-burying behavior, mice were grouped into three clusters and were received 2.5 mg/kg of diazepam or 5, 15, 30, 60 mg/kg of CBD, respectively. (2) To study the implication of 5HT1A receptors in OCD, mice were injected vehicle or 3 mg/kg of the 5HT1A receptor antagonist, WAY100635, and then, 30 min later, mice received vehicle or 10 mg/kg of paroxetine. (3) To investigate the effect of pretreating mice with WAY100635 or CB1 receptor antagonist (AM251) on CBD impacts in the marble-burying behavior, the animals were assigned to clusters that received vehicle or WAY followed by vehicle or 30 mg/kg of CBD after 30 min. Another group was subjected to the same process by 1 mg/kg of AM251. (4) To investigate the impacts of repetitive therapy by CBD or diazepam in the marble-burying test, mice were grouped into clusters injected every day with vehicle, 2.5 mg/kg of diazepam or 30 mg/kg of CBD for seven days. The number of buried marbles decreased by treating with diazepam and 15, 30, and 60 mg/kg of CBD, and paroxetine showed a significant decrease in the marble-burying behavior. The impact of CBD was still significant after seven days, whereas effects of diazepam disappeared afterward. Pretreating by AM251 resulted in antagonizing the influences of CBD on the marble-burying test. However, WAY was not capable of modifying this influence. Besides, CBD had no reducing effect on the locomotor action. Thus, the authors suggested that CBD was inspiring in controlling the compulsive-related behavior. This effect is referred to the facilitation of CB1 receptor-mediated neurotransmission by CBD, which suggests that the endocannabinoid system is involved in the pathophysiology of OCD [45].

3.2.5. Hypericum perforatum (St John's Wort). Hypericum perforatum from the Hypericaceae family, with the common name St John's wort (SJW), is a widely used plant in herbal medicine. SJW extracts showed to have neuroprotective properties [46]. SJW is a natural antioxidant, a valuable reservoir of radical scavenging compounds, and helpful in the prevention and treatment of pathologic disorders related to oxidative stress [47]. Free radical scavenging activity of SJW is due to its Xanthone derivatives and proanthocyanidins [48, 49]. In an animal study, Skalisz et al. evaluated the influence of SJW extract on the marble-burying behavior of mice at dosages that exhibited an antidepressive-like impact but had no increasing effect on locomotor action. In acute experiments, mice received (150, 300, and 500 mg/kg, PO) of SJW extract. In chronic experiments, mice received (300 mg/kg, PO) of SJW extract once a day for 21 days. Results showed that treating animals acutely with SJW (300 and 500 mg/kg) led to a significant reduction in the number of marbles burying behavior, but mice treated chronically (300 mg/kg) were not affected by this treatment [50].

3.2.6. Citrus aurantium (Bitter Orange). Citrus aurantium, called bitter orange or orange blossom from the Rutaceae family, has been traditionally used for several CNS disorders. New research has revealed that bitter orange peel and juice is considered as a natural antioxidant [51]. The ability of this plant to scavenge free radicals is higher than the standard antioxidant, ascorbic acid [52]. An animal study has been conducted by Pultriniet al., who evaluated *Citrus aurantium* essential oil efficacy in OCD on the animal model of marble-burying behavior. Mice received 0.5 or 1.0 g/kg of fruit essential oil acutely by oral route one time daily for 15 days prior to experiments. Treatment of positive control group was done by diazepam (2.0 mg/kg, IP). Tween (10 ml/kg) was selected for the treatment of negative control group. Essential oil and diazepam were efficient in reducing the marble-burying behavior following single and repetitive treatments [53].

3.2.7. Colocasia esculenta (Taro). Colocasia esculenta from the Araceae family, called taro or Elephant ear, is an annual herbaceous plant that has been traditionally used for several diseases. *C. esculenta* possesses robust antioxidant activity but it is less than the standard antioxidant, quercetin [54]. Besides, the boiled tubers of *C. esculenta* contain highly elevated antioxidant property [55]. Kalariya et al. designed an animal study to assess the anticompulsive impacts of the hydroalcoholic extract of *C. esculenta* (HECE) leaves using the marble-burying behavior test in adult male Swiss albino mice. They grouped the mice into separate clusters and administered individual groups with the following drugs: HECE (25 and 50 mg/kg, IP), fluoxetine (5 mg/kg, IP), and

vehicle (1 ml/kg). HECE resulted in a significant reduction in the number of buried marbles. The effect of HECE was comparable with fluoxetine. The authors concluded that the HECE had a dose-dependent anticompulsive effect [56].

3.2.8. Curcuma longa (Turmeric). Curcuma longa, from the Zingiberaceae (ginger) family, has been utilized for decades as a flavoring agent. Curcumin, a yellow pigment, is a natural polyphenol and the major active component of *C. longa* which is a dietary safe phytochemical with numerous salutary effects [57–63]. Curcumin scavenges various ROSs, such as hydroxyl and nitrogen dioxide radicals. Curcumin also has an excessive potential as a lipid-solvable antioxidant that inhibits lipid peroxidation in various animal models [64, 65]. In an animal study by Chimakurthy and Murthy, the effect of curcumin was assessed in the quinpirole-induced model of OCD, and it showed a protective effect on OCD. Adult Wistar rats were grouped into five clusters: group 1 rats received peanut oil (0.1 ml/100 mg) as a control; group 2 rats served as a negative control; in groups 3, 4, and 5, oral treatments of rats were done by 5 and 10 mg/kg of curcumin and 1.8 mg/kg of paroxetine. The entire clusters, except the control group, were treated with quinpirole (0.5 mg/kg, PO). Curcumin lowered obsessive-compulsive symptoms of rats, including repetitive cleansing the snout and grooming, as well as overall length and frequency of stops at objects. Rats treated with curcumin (5 and 10 mg/kg) showed decreased dopamine concentrations, but an elevation occurred in serotonin concentrations only at 10 mg/kg of curcumin [31].

3.2.9. Tabernaemontana divaricata. Tabernaemontana divaricata (Crepe jasmine) from the Apocynaceae family has been used in traditional medicines, frequently for fever, pain, and dysentery. Extracts of this plant could be used as pharmacological interventions in various diseases [66]. The extracts of *T. divaricate* has a significant antioxidant ability. The antioxidant property of *T. divaricata* could arise from their phenolics and flavonoid contents [67]. In an animal study by Chanchal et al., the influence of ethanolic extract of *T. divaricata* leaves was evaluated on burying behavior in adult Swiss albino mice. Seven groups of the animals received the following drugs orally: group 1 normal saline, groups 2, 3, and 4 100, 200, and 300 mg/kg of *T. divaricata*, respectively, and groups 5, 6, and 7 fluoxetine at doses of 5, 10, and 30 mg/kg, respectively. Acute treatments with *T. divaricata* and fluoxetine in a dose-dependent manner led to decreased marble-burying behavior in the animals with no effects on the motor activity. Moreover, they did not show severe side effects [68].

3.2.10. Lagenaria siceraria (Molina). Lagenaria siceraria from the Cucurbitaceae family, with the common name bottle gourd, showed a broad spectrum of pharmacological activities. *L. siceraria* fruit is an important source of natural radical scavengers and antioxidants [69]. Also, the antioxidant property of methanolic extract of *L. siceraria* fruit powder is higher than ascorbic acid. High contents of flavonoids and flavonols could be a reason for this considerable antioxidant activity of *L. siceraria* extracts [70]. Prajapati et al. evaluated the anticompulsive properties of *L. siceraria* methanolic extract through the behavioral test of marble-burying in adult Swiss albino mice. 25 and 50 mg/kg of *L. siceraria* extract were administrated IP. Control group was only treated with vehicle (CMC), and a standard group was administered with fluoxetine (10 mg/kg, IP). Molina at both doses suppressed marble-burying behavior, and its activity corresponded to that of fluoxetine. Results showed that *L. siceraria* possessed dose-dependent anticompulsive activity [71].

3.2.11. Withania somnifera. Withania somnifera or Ashwagandha from the Solanaceae family, commonly named Indian Ginseng, has been utilized to enhance mental and physical health. An *in vitro* study demonstrated that methanolic and ethanolic extracts of *W. somnifera* had significant antioxidant activity. High contents of flavonoids in *W. somnifera* can explain its high radical scavenging activity [72]. The influences of methanolic extract of *W. somnifera* (MEWS) and aqueous extracts of *W. somnifera* (AEWS) were investigated in an animal study by Kaurav et al. The authors used the marble-burying model to assess compulsive behaviors on male Swiss albino mice. Animals were assigned to dissimilar clusters; administrations of fluoxetine (5, 10, and 15 mg/kg), AEWS (10, 25, 50, and 100 mg/kg), and MEWS (10, 25, 50, and 100 mg/kg) were done IP. Administration of AEWS and MEWS (50 mg/kg) lowered the marble-burying behavior frequency with no effect on the motor activity. This influence was comparable to standard fluoxetine [73].

4. Clinical Studies

4.1. N-Acetyl Cysteine. The first systemic review, published by Oliver et al., specifically investigated the application of NAC for the treatment of DSM-5 diagnosed OCD and OCRD patients. They obtained promising findings from 11 studies: five clinical trials and 6 case series. The average period of these studies was 13 weeks, and the number of contributors averaged 19 patients. Treatment with 2400-3000 mg/day of NAC for a minimum of 8 weeks reduced the OCD symptoms and was well tolerable with minimum complications [74]. Smith et al. reviewed systematically the effectiveness of NAC on OCD-related disorders. This review included four methodologically robust clinical trials: OCD: 1, trichotillomania: 2, and onychophagia (nail-biting): 1. The mean trial length with NAC was 11 weeks, and the number of contributors averaged 40 individuals with 800-2,400 mg/day of NAC. Authors observed that the therapeutic outcomes of NAC on OCD and OCRD remained indecisive, along with various reported adverse side effects, from nausea to the development of a full-body rash [75]. Minarini et al. published another systematic review including eleven case series and nine clinical trials on the treatment effects of NAC on OCD and OCRD: Tourette syndrome: 1, trichotillomania: 2, OCD: 3, onychophagia: 1, and excoriation: 2. The mean number of participants was 21 patients. Results showed that the observations remained preliminary; among the disorders mentioned above, excoriation was apparently the most potential

disorder for NAC utilization [76]. Ooi et al. in another study found that a dosage ranging from 2000 to 2400 mg/day could reduce OCD symptoms [77]. In addition to the mentioned studies, new searches were also made for more recent clinical trials. Barroso et al. published the result of treating a male student aged 11 years who had lost his hair because of trichotillomania. Treatment with NAC was initiated with 1200 mg/day during 3 months. This patient showed an apparent improvement, but he could not recover completely. When they increased the dosage to 1800 mg/day, the hairs nearly regrew completely [78]. Kiliç and Keleş reported a case series of three patients with skin-picking, trichotillomania, and nail-biting. The first case was suffering from skin-picking and major depressive disorder. The patient received 225 mg/day of venlafaxine and 1200 mg/day of NAC. Complete discontinue of skin-picking habit was investigated, 3 months following the initiation of NAC. The second case has been addicted to pulling her hair during the past twenty years. Patient was diagnosed with major depression and comorbid trichotillomania. Treatment was initiated with 10 mg/day of escitalopram and, after a second examination, the dose was elevated to 20 mg/d, and NAC was started at a dose of 1200 mg/d. After 1 month, the patient's report indicated that trichotillomania symptoms decreased significantly. The patient's hair loss showed a good improvement in the parietal area of her scalp after 2 months, followed by NAC discontinuation. She was followed up for 6 months, which no extra symptoms were found associated with trichotillomania. The diagnosis of the last case was body-focused repetitive behavior (nail-biting). Treatment was initiated with 1200 mg/day of NAC, which was raised to 1800 mg in the 3rd week. Three weeks after the initiation of the medication, patient reported that nail-biting habit ceased completely. After 6 weeks of the trial, the drug was discontinued and no new symptoms were detected in follow-up examinations [79].

4.2. Minocycline. Minocycline is known for its antioxidant effects, possibly explaining its neuroprotective properties [80]. In a 12-week, prospective, open-label research, Rodriguez et al. assessed an improvement in OCD symptoms through augmenting minocycline with a SRI. Nine patients who met DSM-5 criteria for OCD and ≥16 Y-BOCS scores were enrolled in the study. Subjects received minocycline (100 mg daily) for three days to ensure no allergic reaction and, then, received 200 mg daily for 12 weeks besides their SRI. SRI dose of subjects was constant for a minimum of 12 weeks prior to entering the study. Patients showed no significant differences in YBOCS scores over time. However, two of nine patients who stated that their OCD symptoms started earlier than others showed signs of relief (40% and 46% Y-BOCS reduction). Thus, the authors suggested that augmenting SRI with minocycline might not recover OCD symptoms in every OCD patient but might be effective in those with primary hoarding and early onset of OCD [81]. In a randomized controlled trial (RCT), Esalatmanesh et al. evaluated the efficacy of minocycline as an augmenting agent to Fluvoxamine for the OCD treatment. 102 patients diagnosed clinically with OCD according to the DSM-5-TR and with Y-BOCS scores of ≥21 (mild to acute OCD) participated in their trial. Patients were treated with 200 mg/d of minocycline or placebo for ten weeks. Fluvoxamine (100 mg/day) was administered in the whole patients for the first four weeks and, then, 200 mg/day for the next six weeks, regardless of their treatment groups. At starting point, there were no significant differences in Y-BOCS scores between the two groups, but partial and complete recovery rates were found in the minocycline group at the end of the trial [82].

4.3. L-Carnosine. L-Carnosine (b-alanyl-L-histidine) is a natural neuroprotective dipeptide with antioxidative properties. Also, carnosine decreases mitochondrial ROS [83]. New research has proposed that carnosine is useful for patients undergoing oxidative stress as a highly efficient natural medication without severe side effects [84]. Arabzadeh et al. performed a 10-week RCT to examine the influence of L-carnosine as an adjunct to Fluvoxamine for the therapy of OCD. 44 patients clinically diagnosed with OCD based on the DSM-5 and a Y-BOCS score of ≥21 (mild to moderate OCD) were enrolled to the study. Patients received 1000 mg/day of L-carnosine or placebo as an adjuvant to Fluvoxamine (100 mg/day) for 4 weeks and, then, 200 mg/day of Fluvoxamine for 6 weeks. At starting point, no significant difference was found between the two groups in Y-BOCS total score; however, in L-carnosine group, more significant reductions were recorded in Y-BOCS scores, from baseline to weeks 8 and 10. At the completion of the trial, significant remissions were obtained for 6 patients in the L-carnosine group and 2 patients in the placebo group [85].

Eicosapentaenoic acid (EPA) omega-3 fatty acids are antioxidants [86]. Eicosapentaenoic acid (EPA) is a constituent of omega-3 polyunsaturated fatty acids (PUFAs) present in fish oils. Intakes of PUFAs, such as EPA, may elevate levels of lipoperoxides. PUFAs are more sensitive to oxidation because oxygen can simply attack double bonds [87]. High levels of PUFAs of omega-3 can inhibit ROS, RNS, and the expression of inductive nitric oxide synthase (NOS). PUFAs can regulate the enzymes that are responsible for reactive species production [88]. In an RCT, the effect of adjunct EPA in OCD was evaluated by Fux et al. Participants were 11 patients with existing diagnosis of OCD based on DSM-5, who were on a constant maximal tolerable dosage of SSRI without extra improvements during a minimum of the past 2 months. Patients were assigned to start six weeks of placebo (liquid paraffin, 2 g/day) and then six weeks using 2 g of ethyl EPA. Patients continuously used the same SSRIs dosage. At starting point and at the completion of the trial, the acuteness of OCD was assessed using the Y-BOCS score. Baseline YBOCS score was 26 (5). Average scores dropped to 17.6 (6) in placebo and to 18.5 (4) in EPA group until the 6th week. Results suggested that adjunct EPA was not effective in OCD treatment. The low dose of EPA used in this trial can be the reason for its ineffectiveness [89].

4.4. Folic Acid. Folic acid is used in food fortification, inhibits lipid peroxidation, and is an effective free radical scavenger [90]. In an RCT by Tural et al., the efficacy of adjunct folic acid was assessed in patients with diagnosed OCD. Forty-

three patients with diagnosed DSM-5-TR of OCD were allocated to be treated with a tablet of 5 mg folic acid or placebo with 40 mg of fluoxetine for 12 weeks. Seven patients left the study. Adding folic acid to fluoxetine did not significantly change the Y-BOCS total scores and response rate. The authors concluded that adding folic acid to fluoxetine had no benefits for OCD treatment [91].

4.4.1. Hypericum perforatum (St John's Wort). The efficacy of SJW in treating OCD was assessed in an open-label clinical trial by Kobak and Taylor. Twelve patients were tested with a primary DSM-4 diagnosis of OCD. The treatment continued during 12 weeks, using a constant dosage of 450 mg of 0.3% extended-release formulation of hypericin, a psychoactive compound in SJW, two times a day. The analysis was done every week with the Y-BOCS and the Clinical Global Impressions of Improvement scale (CGI). A significant change was reported, with an average reduction on Y-BOCS of 7.4 points. It changed significantly at the 1st week and continuously increased within the experimental period. In the end, five of 12 were assessed "much" or "very much improved" on the clinician-rated CGI, six were "minimally improved," and one showed "no change." Diarrhea and restless sleep were highly frequent in the reports of side effects [92]. To confirm these results, a 12-week RCT was designed by Kobak and colleagues. Subjects primarily diagnosed with OCD initiated on 300 mg twice daily for 2 weeks, and this dose increased to 1800 mg per day based on the response of the treatment. Sixty subjects were randomized: 30 to SJW and 30 to placebo. Twenty-two and 21 patients in SJW and placebo groups, respectively, completed the study. Outcomes of the study failed to support the effectiveness of SJW for OCD. Based on the Y-BOCS, the average changes of patients with SJW (3.43) was not significantly different with that of placebo (3.60). One of the possible explanations is the differences between the compounds used. The compound formulated here was dissimilar to that utilized in the open-label trial. The highly frequent side effects on SJW were headache, gastrointestinal symptoms, agitation, fatigue, and sleep disturbance [93]. Considering a small sample size in most of OCD trials, it is necessary to have a greater sample size; even so, present studies do not support the usage of SJW in OCD.

4.4.2. Crocus sativus (Saffron). The first RCT on the impacts of saffron in OCD patients was conducted by Esalatmanesh et al. on 50 eligible subjects (saffron = 25, Fluvoxamine = 25) with a Y-BOCS score of 12-21 (mild to moderate OCD). Participants received 30 mg/day of saffron or 100 mg/day of Fluvoxamine for 10 weeks. Results revealed that Y-BOCS diminished significantly in the two groups with no significant intergroup differences, and reported adverse effects were not serious. In this study of *C. sativus* vs. Fluvoxamine, saffron revealed to be as effective and safe as Fluvoxamine [94].

4.4.3. Echium amoenum (Borage). E. amoenum from the Boraginaceae family is a major source of anthocyanins, such as cyanidin and delphinidin [95], which possess important antioxidant activities; however, cyanidin-3-glucoside has been proven to contain more potent antioxidant activities as opposed to the rest of anthocyanins [96]. Borage has a high content of water-soluble antioxidant ingredients [97]. A recent study indicated that using the borage (7 mg/kg two times a day) decreased the LPO (lipid peroxidation level) as an indicator of ROS concentrations [98]. Only one clinical trial evaluated *E. amoenum* in the therapy of OCD. Sayyah et al. examined the efficacy of *E. amoenum* aqueous extract for the therapy of patients with OCD. The score of patients was 21 in the Y-BOCS and were administered no other psychiatric medication within the last 2 weeks prior to the onset of the trial. In this 6 weeks RCT, 44 patients (extract = 24, placebo = 20) randomly received 500 mg/day of *E. amoenum* aqueous extract or placebo. In weeks 4 and 6, the extract group showed statistically significant lower Y-BOCS scores than the placebo group. The authors concluded that aqueous extract of *E. amoenum* could positively affected obsession and compulsion, and these effects started from the 4th week [99].

4.4.4. Silybum marianum (Milk Thistle). S. marianum or milk thistle from the Asteraceae family is a traditional herbal medicine. Silymarin is a flavonolignan extract of the fruits and seeds of this plant species. Silymarin has higher effectiveness than other antioxidant substances. The plant has a minimum of 10 times higher potency than vitamin E [100]. Silymarin scavenges free radicals and chelates metals-promoters including Cu and Fe, suppresses ROS forming enzymes, activates antioxidant enzymes, inhibits lipid peroxidation, and regulates the cell membrane penetrability and stableness [101–104]. Silymarin consists of three flavonoids: silybin (silibinin), silydianin, and silychristin. Silibinin, a compound with the highest biologic activity, is the main constituent present in silymarin [105]. The antioxidant and anti-inflammatory activities of silibinin have been established previously [106]. Sayyah et al., in an eight weeks RCT, evaluated the efficacy of *S. marianum* for the therapy of OCD. Thirty-five patients eligible for the DSM-IV-TR criteria of OCD with a score of at least 21 in the Y-BOCS for OCD, 18 and 17 patients were allocated to the extract and fluoxetine groups. Patients randomly received 600 mg/day of the extract or 30 mg/day of fluoxetine. Findings demonstrated a significantly reduced Y-BOCS in the two groups with no significant intergroup differences. The authors concluded that the effectiveness of both treatments was similar on OCD symptoms. Also, no severe side effects occurred during the treatment [107]. Grant and Odlaug reported the result of a case series of three patients with moderate trichotillomania (National Institute of Mental Health Trichotillomania Symptom Severity (NIMH-TSS) scale = 11), severe contamination obsessions and washing compulsions (Y-BOCS = 22), and nail-biting. Treatment was started with 150 mg of milk thistle two times daily; however, the second case took 300 mg twice daily. After 4 months, NIMH-TSS of the first case was reduced to 3, Y-BOCS of the second case reduced to 12, and the patient became asymptomatic after a rigid treatment for the third case. Results showed the possible potential of milk thistle for the therapy of various compulsive habits [108].

4.4.5. Valeriana officinalis (Valerian). V. officinalis from the Valerianaceae family is widely distributed throughout the world. The essential oils of valerian have moderate antioxidant activity [109]. Putative neuroprotective properties of valerian root extract have been demonstrated in a recent study [110]. Early observations indicate that V. officinalis extract can effectively modulate LPO stimulated by various neurotoxic prooxidant factors [111]. The information can suggest that *V. officinalis* extract may be helpful for the reduction of OCD symptoms accompanying oxidative stress. Pakseresht and colleagues in an RCT, compared the effect of the *V. officinalis* extract with placebo for the therapy of OCD and OCRD. Totally, 31 subjects participated in this trial; 16 and 17 participants were selected randomly for the extract and the placebo group, respectively. The baseline Y-BOCS score of subjects was 21 or higher. Patients were selected to receive 765 mg/day of Valerian extract ($n = 16$) or 30 mg/day of placebo ($n = 17$) for eight weeks. *V. officinalis* effectively reduced the OCD symptoms, and average Y-BOCS scores were decreased in the Valerian group. Patients who were administered the extract achieved statistically significant less scores than the placebo group. The highly frequent adverse effect was drowsiness. The authors concluded that *V. officinalis* had some antiobsessive and compulsive impacts [112].

4.4.6. Withania Somnifera. W. somnifera root extract was usable as a prevention or treatment for stress-related neurologic disorders. The downregulation of neuronal nitric oxide synthase (nNOS) could be the key of its neuroprotection influences [113]. Results of a 6 weeks RCT by Jahanbakhsh and colleagues revealed that the extract of *W. somnifera* might be useful as an adjuvant medication to regularly used therapies of OCD. Thirty patients with a confirmed detection of OCD based on the DSM-5-TR criteria participated in the study and were apportioned to the 120 mg/day of *W. somnifera* extract or the placebo. Patients also received SSRIs at the time of the trial. The acuteness of OCD symptoms was assessed using the Y-BOCS at starting point and at the completion of the trial. Y-BOCS scores had a significant reduction in comparison to placebo. Besides, comorbid anxiety disorder was assessed in this study. However, results showed no significant differences in the reductions of Y-BOCS scores in both treatment and control groups. The authors suggested that the extract of *W. somnifera* might be advantageous as an adjuvant with safety and effectiveness to SSRIs for the therapy of OCD [114].

5. Conclusion

Due to the limitations of the conventionally used pharmacotherapeutic medications for OCD, there is a need for newer strategies to improve the symptoms of the disease. Also, the untoward side effects of SSRIs have triggered an abundance of investigators to assess novel compounds, hoping to find alternate medicines with greater safety. The evidences for the contribution of oxidative stress to OCD are nearly proven but remain indecisive. Antioxidant substances can be capable of improving OCD development because of their anti-inflammatory and antioxidant activities. To our best known, this is the first review of antioxidant drugs investigated for the management of OCD and OCRD. However, a limited number of human studies have been performed on these compounds, and most of them are small pilot clinical trials. In addition, two of the trials with saffron and milk thistle did not have a placebo arm. Well-designed clinical studies with large sample sizes are needed to assess the effective and safe use of antioxidants for the therapy of OCD. Our review presents animal studies, case reports, and clinical studies of antioxidants in OCD treatment, which are available in leading electronic databases, as well as some related systematic reviews. The potential issue in this review was that some medicinal plants with *in vitro* evidences have not been examined in human studies. Another problem was the behavioral test used in animal models. The marble-burying test is probably the most beneficial animal model of OCD among the other tests but this model cannot differentiate between anticompulsive and antianxiety drugs. Also, this test may not respond to all types of anticompulsive drugs. Hence, this is not a perfect model for testing new anti-OCD treatments [115]. Part of the antioxidants reviewed above might establish a novel therapeutic strategy for OCD. In animal studies, herbal medicines have shown a significant reduction in OCD-like behaviors in both acute and chronic treatment. Most RCTs presented in this review were monotherapy with antioxidants, and about three trials used combination therapy with fluoxetine. Moreover, combination therapy with CBT/ERP has not been used in these clinical trials. Among the antioxidant drugs, NAC was one of the most studied drugs on OCD, showing significantly improved OCD symptoms. NAC seems to be effective in trichotillomania; however, more clinical trials are required to confirm the evidence base. NAC apparently has a good extreme tolerance, having minimum adverse effects in comparison to SSRIs. Medicinal plants may have the potential of an efficient monotherapy or augmentation agent besides other approved treatments of OCD, such as SSRIs. Additional investigations are necessary to determine the ability of antioxidants as a standard therapy for OCD, both as an adjunct and a monotherapy.

Data Availability

There is no raw data associated with this review article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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