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Herbal Medicines and Phytochemicals for Obsessive Compulsive Disorder (OCD)

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Abstract

Obsessive compulsive disorder (OCD) is a relatively prevalent mental disorder which poses significant health burdens on the community. Although current conventional medications have good efficacy for many patients, however they can elicit a range of associated adverse effects. Plant-based compounds have been evaluated for different mental disorders, with a range of anxiolytic properties revealed. To determine the current evidence in the area, we conducted a systematic review using the electronic databases including PubMed, Scopus and the Cochrane Library up to June 12 2019 for pharmacological and clinical evidence of herbal medicines and phytochemicals with anti-obsessive-compulsive effects. Additional search criteria were employed for locating research on the under-pinning mechanisms of action. Results revealed that tentative low-quality evidence exists for several plant medicines, including: *Crocus sativus*, *Silybum marianum*, *Echium amoenum*, *Hypericum perforatum* and *Withania somnifera*, along with several natural molecules, including crocin, cannabidiol, and curcumin. While more research is needed to confirm effectiveness, present preclinical studies indicate that monoamine pathway modulation (in particular serotonin reuptake inhibition) may be the most important anti-OCD mechanisms among the studied natural compounds.

1. Introduction

Obsessive-compulsive disorder (OCD) is the fourth most common mental disease, being diagnosed nearly as often as diabetes mellitus and asthma (Prajapati et al., 2011). It is a disabling and distressing mental health problem and is characterized by the presence of obsessions- uncontrollable distressing recurrent thoughts, impulses or images; and compulsions- repetitive behaviors or mental acts that are carried out with the aim to reduce distress (Seibell and Hollander, 2014). The pathophysiology of OCD involves genetic factors and aberrations of the central nervous system (in particular involving the serotonin, glutamatergic and dopaminergic pathways) (Lochner et al., 2004). The lifetime prevalence rate for OCD is approximately 2% in the general population (Zohar et al., 1992), with roughly equal distribution of males and females (Lochner et al., 2004). Some studies suggest that higher annual prevalence of OCD exists in more developed countries such as the USA (1.3%) compared with developing countries such as Taiwan (0.4%) (Weissman, 1998). OCD impacts the patient's quality of life leading to impairments in both personal and professional life (Hollander et al., 2016). Considering the high burden of disease and its socioeconomic adverse effects, there are relatively few treatment options. While cognitive behavioral therapy with exposure and response prevention method (ERP) is a well-established treatment for OCD, however it is not completely effective for some patients (Abramowitz et al., 2007). Selective Serotonin Re-uptake Inhibitors (SSRIs) are the first line medications for OCD, but approximately 40% of patients are resistant and fail to respond (Hollander et al., 2003). Furthermore, treatment with SSRIs is associated with a range of adverse side effects such as insomnia, anxiety and decreased libido and sexual dysfunction

(Jenike, 2004). Medicinal plants are potential sources for identifying new pharmacological interventions for mental disorders (Bahramsoltani et al., 2015, Farahani et al., 2015, Farzaei et al., 2016). Camfield et al. reviewed medicinal herbs and phytochemicals for management of OCD (Camfield et al., 2011) and found a range of plants for this disorder which are acting via modulating two important pathways including glutamatergic and serotonergic pathways. However, this review was conducted 8 years ago, and thus it is timely to provide an update on the present evidence. Thereby the present paper aims to review potential anti-OCD herbal and phytochemicals and their mechanisms of action. For this purpose, a literature search was conducted to identify any *in vivo* or clinical studies of herbal medicines or phytochemicals in the treatment of OCD.

2. Methods

The electronic databases including PubMed, Scopus and The Cochrane Library were accessed up to June 12 2019 for both preclinical and clinical data pertaining to plant medicines and OCD. Language restriction was performed and English language articles were included. The search terms were ("obsessive compulsive disorder" or "obsessive" or "obsessive compulsive") and ("herbal medicine" or "herbal" or "traditional" or "plant" or "phytomedicine" or "complementary") in the title, abstract and keywords. Related articles were screened from the located articles. Articles which were duplicates, reviews, which studied other sorts of obsessions other than OCD, or assessed other complementary medicines other than plant-based medicines, were eliminated. No

restriction was set for design or duration of the study, dose of the plant used, sample size, gender, or location. References of final included studies were reviewed for relevant studies. Final articles were reviewed to extract plant scientific names, part and extract of the plants, presentation of OCD, animal model for *in vivo* and type of clinical trial, number of patients, interventions, duration of treatment and efficacy and tolerability of the herbal treatment for human studies. Results were summarized in **Table 1** and **2**.

3. Results

3.1. Overview

From 1022 articles found, 18 were included in this study (Figure 1). The final result consisted of 11 animal and 7 human studies. Trial lengths were between 6 and 12 weeks with an average sample size of 37 participants (primarily studying cohorts). All the clinical trials used the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) to assess the OCD degree. Y-BOCS is a reliable instrument for measuring the severity and frequency of symptoms in OCD patients. It is a 10 item scale which provides the necessary information with respect to the time spent, interference, resistance, distress, and control over all obsessions and compulsions (Goodman, Price et al. 1989). Each item is scored between 0 to 4 and all the items are summed to obtain a total score ranging from 0 (no symptoms) to 40 (very severe symptoms) (Deacon and Abramowitz, 2005).

All the included clinical trials used the herbal extracts; while different extraction methods were carried out (Table 2). Almost all the trials had gender balance; however,

in some of them one gender was differentially over-represented (Sayyah et al., 2009, Jahanbakhsh et al., 2016). Out of seven clinical trials, five had been conducted in Iran and two in the USA. Out of 11 preclinical studies, nine used marble-burying model to assess obsessive compulsive behaviors. This is a well-known animal model of assessing compulsive-like behaviors which does not require any behavioral training or pharmacological manipulation (Joel, 2006). In the marble burying test, animals are placed in a standard cage filled with 5 cm depth of wood chip bedding with 20 marbles arrayed on top. After thirty minutes the number of marbles buried is scored (Angoa-Pérez et al., 2013). One of the *in vivo* studies applied mCPP (the non-selective serotonin receptor agonist) to induce OCD-like behavior and evaluated the excessive self-grooming in rats (Georgiadou et al., 2012). The remaining study used quinpirole-induced compulsive checking and animals were analyzed to obtain the behavioral measures such as frequency of stops, total duration of stopping, number of visits to other objects and frequency of ritualistic behavior (Chimakurthy and Murthy, 2010).

3.2. Herbal Medicines and Phytochemicals for OCD

***Benincasa hispida* (Thunb.) Cogn.**

Benincas hispida from Cucurbitaceae is commonly known as hairy-melon, winter-melon, wax-gourd, ash-pumpkin or white-pumpkin. It is native to the Asian tropics and usually recognized for its nutritional and medicinal properties especially in China, India and Philippines. *B. hispida* fruit is reported as an important ingredient of some

Ayurvedic medicines, and have been widely used for the treatment of nervous disorders. It is a rich source of triterpenes, phenolics, glycosides and sterols (Zaini et al., 2011). The juice and extract of hairy-melon fruit revealed significant anti-depressant activities (Zaini et al., 2011). It is shown to improve serotonergic function and proposed to be similar to selective serotonin reuptake inhibitors (SSRI) (Kumar and Vimalavathini, 2004; Al-Snafi, 2013). It also had been suggested to have MAO-A inhibiting properties and increase the levels of norepinephrine and dopamine and decrease the levels of GABA as well (Dhingra and Joshi, 2012). It had been suggested to have an anti-OCD potential; however, the exact mechanism through which this may potentially occur is yet to be established. Whilst no human clinical data exist to determine its anti-OCD effect, there is an animal study that shows methanol extract of *B. hispida* fruit exhibited considerable anti-compulsive effect in the marble-burying behavior in mice without affecting motor activity (Girdhar et al., 2010).

Cannabis sativa L. and cannabidiol

Cannabis sativa from Cannabaceae, has been used in traditional Chinese, Indian and Persian medicine for centuries. Cannabidiol (CBD), one of the major constituents of *Cannabis spp.* has recently drawn increasing interest for a range of neuropsychiatric disorders particularly as an anxiolytic and antipsychotic agent (Iffland and Grotenhermen, 2017). It has been also suggested as a novel treatment for OCD. The putative anti-OCD properties of cannabidiol are in part attributed to the indirect modulation of CB1 receptor-mediated neurotransmission, and increased anandamide

levels (Bisogno et al., 2001). CBD also reduces glutamate release in neural pathways involved in compulsive behavior (Piomelli, 2003). Some studies suggest that the effect of CBD on dopamine and GABA levels is associated with its strong antioxidant properties by modulating the expression of nitric oxide synthase and inhibiting the production of ROS-generating NADPH oxidases (Compos et al., 2017). An animal study investigated the effect of CBD on mice in marble-burying test. CBD (15, 30 and 60 mg/kg) decreased the number of buried marbles significantly compared with the control group. Also, the effect of CBD (30 mg/day) remained remarkable after 7 days of repeated daily administration. In this study pretreatment with a 5HT1A receptor antagonist (WAY100635) failed to prevent the effect of CBD. Thus it indicates the mechanisms other than those mediated by serotonin involve in anti-OCD effects of CBD (Casarotto et al., 2010). There are many clinical trials investigating the psychiatric properties of CBD. It has been shown to reduce anxiety and certain psychotic symptoms, and also be potentially useful for addiction (Iffland and Grotenhermen, 2017). Acute and chronic studies of CBD in humans indicate it is a safe molecule with a low adverse effect profile (Machado Bergamaschi et al., 2011). Considering the results of previous pre-clinical study on OCD together with its safety profile in clinical studies, randomized controlled trials are warranted in order to confirm its effectiveness in OCD.

***Citrus* × *aurantium* L.**

Citrus× *aurantium* (known as bitter orange or orange blossom) from Rutaceae is tropical to Asia and has been traditionally used for the treatment of various health

problems. The major active phytochemicals of bitter orange are known to be flavonoids, especially hesperidin, naringin and also alkaloids, mainly synephrine (Suryawanshi, 2011). The volatile oil of bitter orange has been found therapeutically effective in anxiety (Sarris, 2018). Recently the fruit essential oil has been considered to have anti-OCD effects. The major compound in bitter orange essential oil is limonene (97.83%), which is followed by β-myrcene (1.43%). Both these compounds are biologically active in the central nervous system. These effects are suggested to be through involvement of 5-HT_{1A}-receptors (Costa et al., 2013). Bitter orange can improve serotonergic pathways and enhance the effect of serotonin in synaptic clefts (Saketi et al., 2014) which reduces anxiety and obsessive compulsive behavior. While no human studies were located, an *in vivo* study on bitter orange essential oil has been conducted on mice model of marble-burying test. The main compound of the essential oil was limonene (97.83%). The study revealed that oral administration of the fruit essential oil (both in single dose for 30 min and also repeated one for 15 days) could suppress marble-burying behavior in mice (de Moraes Pultrini et al., 2006).

***Clitoria ternatea* L.**

Clitoria ternatea from Fabaceae, commonly known as Butterfly pea, is a well-known Ayurvedic medicine and has been used for various disorders such as anxiety and depression. “Sankhapushpi”, an Ayurvedic medicine, consists of the roots and seeds of *C. ternatea* and had been used as a neurotonic agent (Mukherjee et al., 2008). Recent studies indicate it possesses anxiolytic and antidepressant activity (Boominathan et al.,

2003). While the exact mechanism of *C. ternatea* by which it exerts its neuropsychiatric effects still remains to be clarified, current studies suggest it might be attributed to its serotonergic activity and may affect 5-HT reuptake (Jain et al., 2003; Al-Snafi, 2016). One animal study showed that the ethanol extract of aerial parts could modulate obsessive compulsive behavior via a significant reduction in marble-burying behavior which was comparable to that of fluoxetine. Also sub effective dose of the extract with the sub effective dose of fluoxetine could significantly potentiate the anti-OCD effect of fluoxetine (Shende et al., 2012). Still there is lack of clinical trials on its effectiveness in psychiatric disorders such as OCD.

***Colocasia esculenta* (L.) Schott**

Basionym: *Arum colocasia* L.

Colocasia esculenta from Araceae, commonly known as Elephant ear, is native to hotter parts of India and Ceylon. It has been traditionally used for several diseases and is regarded as a "nerve tonic" (Prajapati et al., 2011). Hydro-alcoholic extract of leaves of *C. esculenta* has revealed neuropharmacological activity in an animal study. It induced anxiolytic and anti-depressant activity, confirming the traditional claims (Kalariya et al., 2010). It also exhibited anti-compulsive effect on mice model in marble-burying test. Intraperitoneally administration of the extract reduced the number of buried marbles dose-dependently, which was similar to the effect of the antidepressant fluoxetine. The neuroprotective activity of *C. esculenta* is suggested to be related to its flavonoids which can increase the 5-HT concentrations in hippocampus (Zhang et al.,

2012; Kalariya et al., 2015). However, the exact mechanism involved in anti-compulsive effects of *C. esculenta* is currently unclear.

Crocus sativus L. and crocin

Crocus sativus (saffron) from Iridaceae, has long been honored as both spice and medicine by Western Asia. The stigma is well-known in traditional Persian medicine for its neuro-modulatory properties specifically as an antidepressant agent (Akhondzadeh, 2007). The psycho-active properties of saffron have been studied in various animal and clinical research models. It had been known to have neuroprotective, anxiolytic and antidepressant effects (Mazidi et al., 2016). More recently saffron has been considered to have potential anti-OCD effects. In an RCT involving mild to moderate OCD patients, saffron extract (alone) was compared with fluvoxamine. The result revealed that saffron reduced Y-BOCS total score and obsession subscale scores comparable to that of fluvoxamine. After 10 weeks, the partial and complete response rates were 69.56% and 34.7% for saffron group and 65.2% and 30.4% for fluvoxamine group, which were not significantly different between two groups (p=1, p=1). The frequency of adverse side effects did not differ significantly between two groups, however, saffron-treated group experienced less headache, constipation, sweating and vomiting. The exact mechanism through which saffron possess anti-OCD effects is still unclear but it may potentially be through inhibition of serotonin reuptake in synapses (Esalatmanesh et al., 2017). Bharate et al. demonstrated neuroprotective activity of saffron against glutamate-induced toxicity (Bharate et al., 2018). Moreover, its main

constituent, crocin, mitigated cell apoptosis and mitochondrial dysfunction in hippocampal neuronal cells (HT22) induced by l-glutamate (Wang et al., 2019). However, Ettehadi et al. reported contrary effects from intraperitoneal administration of different doses of saffron aqueous extract on glutamate brain concentration of rats: reducing effect at 150 mg/kg and increasing effect at 250 mg/kg. It is worthwhile noting that in this study, dose of 50 to 250 mg/kg caused an increase in the release of dopamine. However, the extract had no effect on norepinephrine and serotonin levels (Ettehadi et al., 2013).

Crocin, an active component of *C. sativus*, has recently raised attention for the potential treatment of a range of psychiatric disorders. It had been shown to be safe in oral administration by healthy volunteers (Mohamadpour et al., 2013). Crocin (50 mg/kg) had shown anxiolytic-like effects in the light/dark rat model (Pitsikas et al., 2008). It has been suggested as a potential treatment for the management of OCD. While there is no clinical trial to confirm its efficacy, there is just one *in vivo* study, evaluating anti-OCD properties of crocin in a rat model of OCD. The non-selective serotonin (5-HT) receptor agonist, 1-(3-chlorophenyl) piperazine hydrochloride (mCPP) was used to induce excessive self-grooming. The results revealed that intraperitoneal administration of crocin could reduce the number and duration of grooming. The exact pharmacological mechanism for the effect of crocin on compulsive behavior is still unknown, however it may act as an antagonist of 5-HT2C receptors (Georgiadou et al., 2012). The neuropsychiatric properties of saffron and crocin can be attributed partly to their high anti-oxidant activities (Lopresti and Drummond, 2014)

Curcuma spp. and Curcumin

The genus *Curcuma* from Zingiberaceae, is native to tropical and subtropical regions, and is mainly distributed in Thailand, China, India, Malaysia, Indonesia, and Northern Australia (Ayati et al., 2019). The rhizome of different species of *Curcuma* had been largely used in different traditional medicines for many diseases. Xiaoyao-san is a traditional Chinese medicine which contains *C. longa* as a major constituent, and has been used for the treatment of stress and depression (Xu et al., 2005). In Persian traditional medicine, *C. zedoaria* is recommended against neural diseases such as epilepsy and is known to have purported neurotonic activities (Ayati et al., 2019). Curcuminoids, which are the most important constituents of *Curcuma*, have a modulatory role on serotonin, dopamine and norepinephrine in different regions of brain and also reported to inhibit the biogenic amines by inhibiting MAO-A and B (Kulkarni and Dhir, 2010). It has shown to be beneficial in different central nervous systems disorders such as epilepsy and depression (Xu et al., 2005, Jithendra et al., 2008). Curcumin has the potential for the treatment of psychiatric disorders by increasing the serotonin levels in the brain (Kulkarni et al., 2008). It has also been reported to have considerable anti-oxidant activity which might be partly involved in its neuropsychiatric activity (Ayati et al., 2019).

In an animal model study on the effect of curcumin on OCD, curcumin showed a protective effect in OCD with considerable influence on brain monoamine levels. Serotonin levels were increased and dopamine levels were decreased in curcumin-treated rats. It also reduced obsessive-compulsive symptoms such as repeated cleaning

the snout and grooming and reduced total duration and frequency of stopping at different objects. Curcumin also showed a considerable retention of memory (Chimakurthy and Murthy, 2010).

***Echium amoenum* Fisch. & C.A.Mey.**

Echium amoenum from Boraginaceae, is an important medicinal plant in Iran which had been used for centuries and mostly known as an anxiolytic and anti-depressant remedy (Sayyah et al., 2009). There are some animal and clinical trials confirming the anxiolytic and antidepressant activities of this plant (Sarris et al., 2011). Recently some studies have also revealed its potential anti-OCD effects. An aqueous extract of *E. amoenum* demonstrated anti-OCD activity via increasing the level of cerebrospinal fluid CSF serotonin and dopamine (Faryadian et al., 2015). An RCT involving OCD patients has been conducted in Iran, evaluating the effect of aqueous extract of *E. amoenum* flowers on obsessive compulsive behavior using Y-BOCS scale. As anxiety is a common symptom of OCD, Hamilton Rating Scale for Anxiety (HAM-A) was also used. No other psychotropic medication was prescribed. Results revealed that in weeks 4 and 6, participants treated with the extract had significantly lower Y-BOCS scores than the placebo-treated participants. HAM-A scores were also significantly lower in the extract group in weeks 4 and 6, which indicate anxiolytic effects of *E. amoenum*. There was no significant adverse side effect associated with *E. amoenum* administration (Sayyah et al., 2009). While *E. amoenum* had shown to increase dopamine and serotonin, and the preliminary RCT reported its efficacy, further RCTs with a larger sample size and longer duration are warranted to confirm its potential efficacy.

***Hypericum perforatum* L.**

Hypericum perforatum from Hypericaceae, commonly known as St John's wort (SJW), is native to Europe and Asia. It is best known for its antidepressive activity, and had revealed significant results equivalent to conventional antidepressants (Rahimi et al., 2009; Sarris and Kavanagh, 2009). The antidepressant effect of SJW is due to a range of neuro-pharmacological effects, including re-uptake inhibition of monoamines and improving the sensitization and binding to receptors (e.g. 5-HT) (Camfield et al., 2011). Some studies report that after SJW administration, a preferential increase of serotonin is more prominent than norepinephrine and dopamine (Calapai et al., 2001). The neurobiological active constituents of SJW are considered to be hyperforin, hypericin and pseudohypericin. Hyperforin has been revealed as a reuptake inhibitor of 5-HT, dopamine, GABA, norepinephrine and L-glutamate in synapses (Barnes et al., 2001). Hypericin has shown to increase the hypothalamus 5-HT concentrations after 8 weeks' administration, however there are issues with this compound crossing the blood brain barrier (Butterweck et al., 2002). Other mechanism of action associated with active constituents of SJW is known to involve monoamine oxidase (MAO) inhibition (Camfield et al., 2011).

The effect of SJW on monoamine transmission may have a potential effect in the treatment of OCD. In a preclinical study on mice, acute treatment with SJW significantly reduced the number of marbles burying behavior, however chronic treatment didn't maintain this effect (Skalisz et al., 2004). Due to this preclinical efficacy, SJW was assessed in an initial open label pilot clinical study on OCD patients

(without using any conventional medications). A significant improvement was found at the end of the study and the mean Y-BOCS score changed 7.4 points. The score changes started as early as one week and increased over time. Diarrhea and restless sleep were the most common reported side effects (Taylor and Kobak, 2000). To confirm these results, an RCT was performed by the same research group. Results in this placebo-controlled study however revealed no significant differences on Y-BOCS. Also the difference between SJW and placebo on any of the Y-BOCS subscales was not significant (Kobak et al., 2005).

***Lagenaria siceraria* (Molina) Standl.**

Lagenaria siceraria from Cucurbitaceae, commonly known as Bottle gourd is an Ayurvedic and Chinese herbal medicine. The fruits are traditionally used in India for the treatment of a range of diseases, and especially for cardiovascular and hepatic disorders (Shah et al., 2010). The fruit has been considered to have neuropsychiatric properties. It has been suggested that the flavonoids or steroidal compounds of *L. siceraria* might be the responsible phytochemicals for its neuropharmacological activities (Prajapati et al., 2011). Pretreatment of the fruit ethanol extract has ameliorated the stress in a forced swimming endurance stress and acute heat stress rat model, indicating an anti-stress and adaptogenic activity of the plant (Palamthodi and Lele, 2014). *Lagenaria siceraria* is also known to have antidepressant activity (Prajapati et al., 2011). It has been proposed to have anti-OCD properties; however, there is just one preclinical study to date evaluating this. The study was conducted on mice model of OCD, using marble-burying behavior. Intraperitoneal administration of

methanolic extract of *L. siceraria* was compared with fluoxetine. *L. siceraria* at both dosages suppressed marble-burying behavior and the effect was comparable to that in fluoxetine (Prajapati et al., 2011).

***Silybum marianum* (L.) Gaertn.**

Silybum marianum from Asteraceae, better known as milk thistle, is a traditional Mediterranean herbal medicine used most prominently for hepatic disorders, while it is also suggested as a potential remedy for anxiety and OCD (Sarris, Camfield et al., 2012). It enhances serotonergic activity at least partly by modulating 5HT1A receptors (Camfield et al., 2011; Yaghmaei et al., 2012). The putative anti-OCD and anxiolytic-like activities of milk thistle can be related to silymarin, a flavonoid complex, which is reported to enhance serotonin concentration in the brain cortex (Camfield et al., 2011; Solati et al., 2012). This can be attributed to the inhibition effect of silibinin on MAO activity (Camfield et al., 2011). The results of an RCT using milk thistle leaf extract versus the antidepressant fluoxetine in participants with OCD demonstrated a significant reduction on Y-BOCS in both groups without any significant difference between them. No serious adverse effect was associated with milk thistle administration (Sayyah et al., 2010). In consideration of the small sample size and unstandardized preparation used in this study, RCTs with larger populations (and standardized formulations) are now required.

***Tabernaemontana divaricata* (L.) R.Br. ex Roem. & Schult.**

Tabernaemontana divaricate (TD) from Apocynaceae, is a common plant in tropical countries and have been used in Chinese, Ayurvedic and Thai traditional medicines, mostly for fever, pain and dysentery (Pratchayasakul et al., 2008). In Thai traditional medicine, it is also suggested as components of rejuvenating and neuro-tonic remedies to improve memory (Chanchal et al., 2015). The methanol extract of TD showed antidepressant effect *in vivo* (Faruq, Munira et al.). Phytochemical studies have revealed the presence of phenolic compounds, alkaloids, steroids, flavonoids, saponins and terpenes in the plant (Chanchal et al., 2015), so it is presumed that the mechanism of anti-compulsive action of TD can be due to involvement of any of these phytochemicals in serotonergic neurotransmission. Acute treatment with ethanol extract of TD leaves inhibited obsessive and compulsive behavior in mice in a dose dependent manner. The inhibitory effect of TD on obsessive and compulsive behavior was similar to fluoxetine. No serious side effects were associated with the administration of TD (Chanchal et al., 2015). Although the initial evidence in relation to TD in the treatment of OCD is encouraging, controlled clinical trials are warranted so as to properly investigate its efficacy.

***Valeriana officinalis* L.**

Valeriana officinalis from Caprifoliaceae, commonly known as valerian, has been used in traditional medicines of different regions for a long time (Mikaili et al., 2011). It has been reported that valerian increases the serotonin concentration in brain. Valerian contains constituents with a range of neuromodulatory activities such as anxiolytic and soporific effects. Valeric acid is one of the phytochemicals which has been shown to

inhibit GABA breakdown in the central nervous system and causes muscle relaxation. The roots also contain lignans which inhibit serotonin binding. Valerian root extract had shown a potent anxiolytic effects in rats (Sarris et al., 2011; Neamati et al., 2014). It has been proposed as a potential treatment for OCD. The anti-OCD mechanism of valerian may be attributed to GABA reuptake and serotonin binding inhibition. Eight weeks administration of valerian root extract to participants with OCD significantly lowered Y-BOCS compared to the placebo group. The overall frequency of side effects was not significantly different between two groups. However, somnolence was the most common adverse effect in valerian group (Pakseresht et al., 2011).

***Withania somnifera* (L.) Dunal**

Commonly known as Indian Ginseng or Ashwagandha, *W. somnifera* from Solanaceae, is one of the most well-used Ayurvedic medicinal herbs for thousands of years. The root of *W. somnifera* has been studied as adaptogenic, anxiolytic, antidepressant, neuroprotective and cognitive enhancing agent. It has been reported several times to pose neuroprotective improvement, which can be attributed to its role in nNOS down regulation and neurochemical alteration of some neurotransmitter systems (Bhatnagar et al., 2009). It contains a range of active constituents including withanolides, sitoindosides and other alkaloids. The anxiolytic effects are attributed to the presence of bioactive glycol-withanolids (Bhattacharya et al., 2000). In an RCT involving 64 patients, 300mg of *W. somnifera* root extract for two months, effectively reduced the anxiety, serum cortisol, social dysfunction and depression in participants with a history of chronic stress (Chandrasekhar et al., 2012). Administration of *W. somnifera* root

extract to patients with OCD that were receiving SSRIs simultaneously caused significant reduction in Y-BOCS score in treatment group compared to the placebo group. In this study, the effect of *W. somnifera* was also evaluated on patients with comorbid anxiety disorder. These patients were analyzed separately in the treatment and control groups and the reduction of Y-BOSC score was compared between patients with and without comorbid anxiety in each group. The reduction of Y-BOCS score in both treatment and control groups was not significantly different between patients with comorbid anxiety or those without anxiety. The extract was reported to be safe, with no adverse events revealed during the trial (Jahanbakhsh et al., 2016). While in this trial the results from the effect of *W. somnifera* on OCD are encouraging, considering the small number of participants (15 patients in each group), a larger scale RCT is required.

4. Discussion

Considering the partial effectiveness, potential side effects and therapeutic delay in symptom improvement observed with conventional pharmacotherapeutic treatments for OCD, it is timely to advance more robust research into plant-based treatments either as potential monotherapy or augmentation strategies. To our knowledge, since 2011, this is the most recent comprehensive systematic review of herbal medicines and phytochemicals investigated for the management of OCD and their plausible mechanisms of action. This review has some results in common with other previous review articles (Camfield et al., 2011; Sarris et al., 2012; Sarris, 2018), however more recent studies are included in the present article.

Although the study on anti-OCD herbal and phytochemicals is in its infancy, the results are encouraging. Among the herbal medicines, *C. sativus*, *E. amoenum*, *W. somnifera*, *V. officinalis* and *S. marianum* showed a significant improvement in OCD patients. However, small sample sizes and short study durations, and unreplicated trials, limit confidence for many medicinal plants. Additionally, some of the herbal medicines (e.g. *B. hispida*, *C. aurantium*, *C. ternatea* and *C. esculenta*) along with all the investigated phytochemicals (crocin, curcumin and cannabidiol) have been just evaluated in animal studies. *H. perforatum* was one of the most studied plant on OCD which was evaluated both *in vivo* and by two RCTs; however as detailed in table 2, the evidence concerning SJW does not support its use in treating OCD. *E. amoenum* was evaluated in a parallel RCT and revealed encouraging results, by both reducing OCD and anxiety symptoms, confirming its traditional uses.

Certain herbal medicines such as *C. sativus*, *V. officinalis* and *E. amoenum* offer preliminary evidence for the treatment of OCD, through known psychopharmacological actions, including re-uptake inhibition of monoamines (such as serotonin and dopamine), GABAergic effects, and neuro-endocrine modulation. In the case of some studied herbs such as *S. marianum* or phytomedicine-derived compounds like cannabidiol, the anti-OCD mechanisms of action are not clearly defined, having a multitude of biological effects.

While the literature reviewed in this study provides encouraging, albeit tentative, evidence for the use of medicinal plants and phytochemicals for the treatment of OCD, it is recognised that many studies are unreplicated with small sample sizes. The limited

data on the clinical effects of herbal medicines and phytochemicals for the treatment of OCD can be related to the challenges in terms of accurate assessment via the YBOCS due to some patient's not having an accurate insight into their condition. Considering the low number of human studies and their various limitations such as small number of participants and low methodological quality, confidence in the evidence detailed in this review needs to be tempered. Another potential issue is that some herbal medicines with *in vivo* evidence have not yet been rigorously tested in robust human studies. Thus, further research involving RCT designs are still required to obtain ensuring results in their effectiveness.

There are some safety considerations about the use of the mentioned herbal medicines. While most of the reviewed medicinal plants, such as *C. sativus* and *S. marianum*, are considered to be safe in usual dosages (Tamayo and Diamond, 2007; Modaghegh et al., 2008), there are some deficiencies regarding the safety data of the others. Although some studies evaluated the acute and sub-chronic toxicity of some medicinal herbs such as *L. siceraria* in animal models (Saha et al., 2011), safety evaluation in human clinical trials is required to be considered confidently for regular prescriptive application.

Further, potential drug interactions should also be considered. SJW extracts which are rich in hyperforin has shown to induce P-glycoprotein transporter (P-gp) and a range of CYP450 coenzymes such as CYP3A4, CYP2C19 and CYP2C9, and can affect the metabolism of different drugs (Soleymani et al., 2017). Some of the antidepressants (e.g. amitriptyline), cardiovascular drugs (e.g. digoxin), anti-coagulants (e.g. warfarin) and lipid-lowering drugs (e.g. atorvastatin) are among the medications whose plasma

concentrations (and potential effectiveness) are lowered from concomitant administration with high-hyperforin SJW medicines (Rahimi and Abdollahi, 2012).

Our review presents several strengths. It includes its coverage of both pre-clinical and clinical studies of herbal medicines and phytochemicals for treating OCD, which were published in three of major electronic databases with their plausible mechanism of actions. We do however recognize some limitations. Firstly, due to language constrains, only English language articles were included in this review and there may be published studies in languages other than English.

In summary, a number of herbal medicines may potentially be effective as monotherapies or augmentation therapies in the treatment of OCD. Furthermore, some phytochemical isolates exhibited anti-OCD effect. The studied phytochemicals showed their activity by different mechanism including serotonin elevation, glutamate modulation and antioxidant activity. Future research is suggested to also be centered on combination of herbal medicines with pharmacological and clinical evidence of efficacy. While monotherapy is usually the gold standard methodology, combination or augmentation therapy may also be of merit.

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Conflict of interest

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Contributors

R.R. and Z.A. provided the conception and design. Z. A. carried out the searching and data collection and took the lead in writing the manuscript. R. R. and J. S. supervised the project and contributed to the interpretation of findings. S. A. E. oversaw related pharmacognosy issues. D. C. contributed in pharmacological interpretation. All authors provided critical review, and approved of the final submission.

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Table 1: Animal studies on the use of medicinal plants for obsessive compulsive disorder

Scientific name	Part/Extract/ Phytochemical	Model	Animal	Dosage (mg/kg)	Study design	Result	References
Benincasa hispida	fruit/methanol extract	marble-burying model	male Swiss albino mice	200, 400, 600	*in vivo*	↓ marble-burying behavior (400, 600 mg/kg), no effect on motor activity. (*$p < 0.0001$), no significant difference in motor activity ($p = 0.7807$) ↓ marble-burying behavior (extract (200 mg/kg) + fluoxetine (5mg/kg)) (*$p < 0.001$)	(Girdhar et al., 2010)
Cannabis sativa	cannabidiol	marble-burying model	male mice	15, 30, 60	*in vivo*	↓marble burying behavior activity (*$p \leq 0.05$)	(Casarotto et al., 2010)
Citrus aurantium	fruit/ essential oil	marble-burying model /light – dark box test/ rotarod test	Swiss albino mice	500 or 1000	*in vivo*	the time spent in the light compartment (Single treatment (ST): ↑, Repeated treatment (RT): no effect); the number of transitions between chambers (ST: ↑, RT: no effect), the number of rearings (ST: no significant modification), the number of buried marbles (ST: ↓ (*$p \leq 0.05$), RT: ↓ (*$p \leq 0.05$))	(de Moraes et al., 2006)
Clitoria ternatea	dried aerial parts /ethanol extract	marble-burying model	male Swiss albino Mice	100, 200, 400	*in vivo*	↓marble-burying behavior (*$p \leq 0.05$), no effect on motor activity	(Shende et al., 2012)
Colocasia esculenta	leaves /hydro alcohol extract	marble-burying model	male Swiss albino mice	25, 50	*in vivo*	↓number of buried marbles (*$p \leq 0.05$)	(Kalariya et al., 2015)
Crocus sativus	crocin	mCPP induced OCD like behavior (excessive	male Wistar rat	30, 50	*in vivo*	↓number of grooming episodes (*$p < 0.05$), ↓duration of grooming events (*$p < 0.05$)	(Georgiadou et al., 2012)

		self-grooming assessment)					
Curcuma longa	curcumin	quinpirole induced obsessive-compulsive	rat model	5, 10	*in vivo*	↑brain serotonin, ↓brain dopamine, ↓duration and frequency of stopping at respective objects, ↓ritual-like behaviors (*$p < 0.05$)	(Chimakurthy and Murthy, 2010)
Lagenaria siceraria	fruit /methanol extract	marble-burying model	Swiss albino mice	25, 50	*in vivo*	↓marble-burying behavior (*$p < 0.001$)	(Prajapati et al., 2011)
Hypericum perforatum	aerial parts/extract	marble-burying model/forced swimming test	male Swiss albino mice	150, 300, 500	*in vivo*	the number of marbles buried (acute treatment (AC):↓ (*$p < 0.02$), chronic treatment (CC): no effect ($p > 0.10$)), locomotor activity (AC and CC: no effect ($p > 0.10$)) , immobility time (AC): ↓(*$p < 0.05$)	(Skalisz et al., 2004)
Tabernaemontana divaricata	leaves/ ethanol extract	marble-burying model	Swiss albino mice	100, 200, 300	*in vivo*	↓marble-burying behavior in mice (*$p < 0.0001$), no effect on motor activity ($p = 0.7771$)	(Chanchal et al., 2015)
Withania somnifera	root/ methanol extract (MEWS) and aqueous extract (AEWS)	marble-burying model	Swiss albino mice of both sexes	50 (MEWS); 10, 25, 50, 100 (AEWS)	*in vivo*	↓number of marble burying behavior activity with AEWS (except with 10 mg/kg) (*$p < 0.001$) and MEWS (*$p < 0.0001$)	(Kaurav et al., 2012)

Note: The ↑ and ↓ signs indicate significant increase ($p \leq 0.05$) and significant decrease ($p > 0.05$).

Table 2: Clinical studies on the use of medicinal plants for obsessive compulsive disorder

Scientific name	Part/Extract/ Phytochemical	Type of study	Intervention	Number of participants	Concomitant drugs	Duration (weeks)	Results	References
Crocus sativus	stigma/extract	randomized -double blind	saffron 30 mg/day (15 mg twice a day) or fluvoxamine 100 mg/day	50	---	10	↓Y-BOCS, no significant difference between two groups (p = 0.47)	(Esalatmanesh et al., 2017)
Echium amoenum	flowers/aqueous extract	randomized -double blind, placebo controlled, parallel-group	500 mg/day	44	---	6	↓Y-BOCS (*p = 0.035), ↓ anxiety symptoms ($P < 0.05$)	(Sayyah et al., 2009)
Hypericum perforatum	aerial parts/extract	open-label trial	450 mg (extended-release), twice a day	12	---	12	↓Y-BOCS (*p = .001)	(Taylor and Kobak, 2000)
	aerial parts/hydro alcoholic extract	multi central, randomized double-blind – placebo controlled, parallel group	flexible-dose schedule (600–1800 mg/day)	60	---	12	no significant differences between John's wort and placebo at the mean change on the Y-BOCS (p = 0.899)	(Kobak et al., 2005)
Silybum marianum	leaves/methanol extract	pilot double-blind randomized trial	200 mg 3 times a day	35	fluoxetine 10 mg 3 times a day	8	↓Y-BOCS (*p = 0.0001), no significant difference between the extract and fluoxetine (p = 0.94), positive effects of the extract on obsession and compulsion	(Sayyah et al., 2010)
Valeriana officinalis	root/extract	randomized double-blind – placebo controlled	765 mg/day	31	---	8	significant OCD improvement (*p=0.000), rapid onset of action	(Pakseresht et al., 2011)

Withania somnifera	root/ethanol extract	randomized double-blind placebo-controlled	120 mg/day	30	SSRIs	6	↓Y-BOCS (*$p < .001$)	(Jahanbakhsh et al., 2016)

Note: The ↑ and ↓ signs indicate significant increase ($p \leq 0.05$) and significant decrease ($p > 0.05$).

Conflict of interest

As a medical research institute, NICM Health Research Institute receives research grants and donations from foundations, universities, government agencies, individuals and industry. Sponsors and donors also provide untied funding for work to advance the vision and mission of the Institute. The authors declare no competing financial interests.

Contributors

R.R. and Z.A. provided the conception and design. Z. A. carried out the searching and data collection and took the lead in writing the manuscript. R. R. and J. S. supervised the project and contributed to the interpretation of findings. S. A. E. oversaw related pharmacognosy issues. D. C. contributed in pharmacological interpretation. All authors provided critical review, and approved of the final submission.

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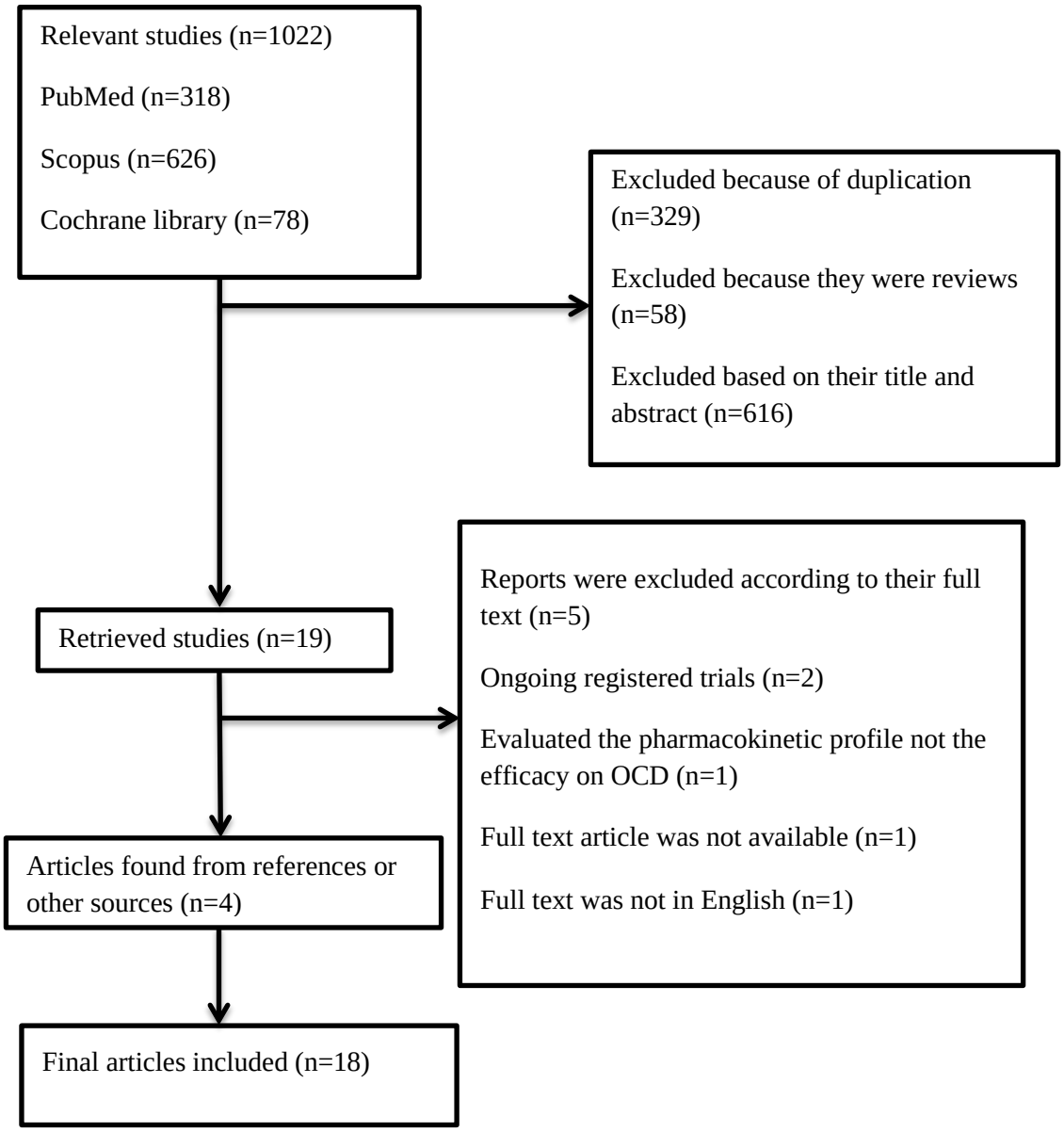

Figure 1: Study selection diagram