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S-adenosyl-L-methionine (SAMe), cannabidiol (CBD), and kratom in psychiatric disorders: Clinical and mechanistic considerations

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ABSTRACT

Given the limitations of prescription antidepressants, many individuals have turned to natural remedies for the management of their mood disorders. We review three selected natural remedies that may be of potential use as treatments for depressive disorders and other psychiatric or neurological conditions. The best studied and best supported of these three remedies is S-adenosyl-L-methionine (SAMe), a methyl donor with a wide range of physiological functions in the human organism. With the increasing legalization of cannabis-related products, cannabidiol (CBD) has gained popularity for various potential indications and has even obtained approval in the United States and Canada for certain neurological conditions. Kratom, while potentially useful for certain individuals with psychiatric disorders, is perhaps the most controversial of the three remedies, in view of its greater potential for abuse and dependence. For each remedy, we will review indications, doses and delivery systems, potential anti-inflammatory and immunomodulatory action, adverse effects, and will provide recommendations for clinicians who may be considering prescribing these remedies in their practice.

1. Introduction

Depression remains a difficult to treat disorder. Among people with major depressive disorder (MDD), about half will not respond to registered therapies, and many of those who do respond will eventually experience relapses and recurrences (Kennedy, 2013). Because of the limitations of currently approved antidepressants, natural remedies have been an increasingly popular alternative therapy for individuals with difficult to treat depression (National Institutes of Health, 2010). Natural remedies have been used throughout the world for thousands of years and have been growing in popularity in the United States and much of the industrialized world over the past 2–3 decades. Widely used natural remedies include St. John's wort and omega-3 fatty acids for depression, melatonin and valerian for insomnia, kava for anxiety, and ginkgo biloba for dementia, among many others. Along with growing evidence for clinical efficacy of different herbal and natural remedies, recent research efforts have increasingly focused on their potential mechanisms of antidepressant action, including the interaction between inflammatory activity, depressive symptoms, and behavioral effects.

In this article, we will review three selected natural products with potential relevance to mood disorders. The first, S-adenosyl-L-methionine (SAMe), has a relatively well-established body of evidence in its support as a treatment for MDD in addition to other neuropsychiatric disorders (Gao et al., 2018). The other two remedies, kratom and cannabidiol (CBD), are newer to the field. Although used for many years in various ways, including recreationally, they are much less well characterized from the standpoint of clinical efficacy for specific disorders, and their potential mechanisms of psychotropic action also require a better understanding. We selected these remedies for review because of their relevance to the theme of this special issue, particularly immunity, and based on their clinical relevance in view of the well-established interest in SAMe and growing interest and use of CBD and kratom, especially in the United States.

Our review is selective, and not intended to be exhaustive or systematic (for example, there are several such reviews of SAMe available), but to provide a concise synthesis of these three natural products, to review the evidence for them as potential mood enhancers/

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antidepressants, to understand what is known about their mechanisms of action, particularly their impact on immune and inflammatory systems in humans, and to provide clinical recommendations for practitioners.

In selecting the literature to be covered, the authors have had ample experience writing about SAMe and began by examining previous reviews. A PubMed search was also carried out using the terms "SAMe," "S-Adenosyl methionine" and "depression" to identify any articles more recent than those previously covered. For CBD and kratom, which comprise a more modest literature, a more simplified search of terms "cannabidiol", "CBD", and "kratom" were used, along with the term "psychiatric" to circumscribe the search. Articles were reviewed by the entire author team for relevance regarding mechanistic as well as clinical data and selected for inclusion on this basis.

For each remedy we will review: 1) Clinical indications and evidence of efficacy; 2) Dosing and delivery systems; 3) Proposed mechanisms of action, particularly those relevant to immunoregulation and effect on the brain; we will include findings from in vitro and animal studies as relevant and from human studies where available; 4) Adverse effects, particularly concerns about risk of abuse/dependence with Kratom and CBD; and 5) Recommendations for practitioners who may be considering prescribing these treatments, or whose patients may already be using them on their own.

2. S-adenosyl-L-methionine (SAMe)

2.1. Clinical indications and evidence

Since its discovery in 1952, SAMe has been found to play roles in multiple crucial biochemical pathways and has been indicated for use in central nervous system (CNS) diseases (Gao et al., 2018; Sharma et al., 2017). The most encouraging neuropsychiatric indications include major depressive disorder (MDD), with evidence for SAMe as an effective monotherapy as well as an adjunct therapy (Alpert et al., 2004, Papakostas et al., 2010). Efficacy as monotherapy was supported by superiority to placebo in 12 randomized placebo-controlled trials (RCTs), and equal or superior effects to other antidepressants in 18 RCTs. SAMe adjunctive therapy in combination with other antidepressants (including tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs], and serotonin-norepinephrine reuptake inhibitors [SNRIs]) is supported for the treatment of MDD and for non-responders to standard antidepressants (Sharma et al., 2017). Two recent open-label trials, however, were negative, perhaps in part due to underdosing of SAMe (Sarris et al., 2018, Sarris et al., 2019).

Cognitive impairment is frequently associated with MDD. SAMe augmentation of SSRIs is potentially indicated for treatment of memory-related cognitive impairment (recall of information and word finding) (Levkovitz et al., 2012), and SAMe may also have benefits in cognitive decline seen in dementia (Shea and Chan, 2008). One RCT of SAMe augmentation showed that SAMe may alleviate sexual dysfunction secondary to depression or standard antidepressant medication (Dording et al., 2012).

SAMe may also have benefit in the treatment of depression associated with other medical conditions. These may include HIV, with effectiveness established by one open-label study (Shippy et al., 2004); Parkinson's disease, supported by one open-label study (Di Rocco et al., 2000) and two RCTs (Sharma et al., 2017); hepatitis or cirrhosis associated with substance use disorders, supported by two clinical trials (Sharma et al., 2017), and indirectly suggested by its attenuation of liver injury in alcoholic liver disease (ALD) (Diaz Belmont et al., 1996; Mato et al., 1999; Vendemiale et al., 1989). SAMe alone or in combination with ursodeoxycholic acid (UDCA) has been supported for treating intrahepatic cholestasis of pregnancy, suggesting safety in depressed women during pregnancy and post-partum. Efficacy was shown by one single-blind clinical trial (Frezza et al., 1984), and 10 RCTs (Binder et al., 2006a,b; Floreani et al., 1996; Frezza et al., 1990; Frezza et al., 1984; Frezza et al., 1988; Roncaglia et al., 2004; Zhang et al., 2015).

SAMe may be effective for the treatment of chronic pain in osteoarthritis, and both pain and depression associated with fibromyalgia. In osteoarthritis, efficacy was established by eight placebo-controlled RCTs (Berger and Nowak, 1987; Bradley et al., 1994; Caruso and Pietrogrande, 1987; Glorioso et al., 1985; Maccagno et al., 1987; Muller-Fassbender, 1987; Schumacher, 1987; Vetter, 1987), one long-term clinical trial (Konig, 1987), and equivalence in two RCTs comparing SAMe against nonsteroidal anti-inflammatory drugs (NSAIDs) (Kim et al., 2009; Najm et al., 2004). In fibromyalgia, efficacy was established in four double-blind clinical trials (Jacobsen et al., 1991; Tavoni et al., 1998; Tavoni et al., 1987; Volkmann et al., 1997).

SAMe alone or in combination with other nutraceuticals is thought to improve cognitive function and reduce aggressive behavior in dementia or Alzheimer's disease. Efficacy was partly supported by two open-label studies (Chan et al., 2008; Remington et al., 2009) and one RCT (Remington et al., 2015). SAMe alone or adjunctively may reduce aggression in schizophrenia, per one pilot RCT (Strous et al., 2009). SAMe may promote recovery from behavioral, sensory and histological disturbances due to brain/nerve damage, per several preclinical trials (Gregoire et al., 2017; Rao et al., 1997; Takahashi et al., 1986, 1987; Villalobos et al., 2000). Similarly, SAMe's antiepileptic effect may suggest a role in treating seizure disorders, per several preclinical trials (Dhediya et al., 2016).

General areas of influence of SAMe are illustrated in Fig. 1.

2.2. Dosing and delivery methods

Historically SAMe was delivered in two parenteral forms: intravenous (IV) and intramuscular (IM). Several early studies in MDD reported that efficacious doses of SAMe were 200–400 mg/day IV and 45–50 mg/day IM. Since the 1990s, oral SAMe (e.g. MSI-195) has been the most commonly used form. According to evidence from later RCTs of SAMe in MDD, oral doses of 800–1600 mg/day showed greater efficacy as monotherapy and as antidepressant augmentation (Deligiannidis and Freeman, 2014). Common oral doses in the treatment of the other conditions listed above varies from 200 mg/day to 1600 mg/day. A relatively high dose of SAMe (1600 mg/day to 4000 mg/day) was used in the treatment of depression associated with Parkinson's disease (Sharma et al., 2017). The mechanism underlying SAMe's efficacy in this population is unclear and needs to be further explored.

The usual starting dose of oral SAMe is 400 mg/day (200 mg/day in elderly, frail, or otherwise vulnerable patients). After assessing for symptomatic improvement in during the first 1–2 weeks, SAMe can be escalated gradually by 200–400 mg/day every 5 to 7 days to a maximum of 800 mg twice daily (Bottiglieri, 2013). One study in MDD reported a dose as high as 3200 mg/day as safe and well tolerated (Mischoulon et al., 2014).

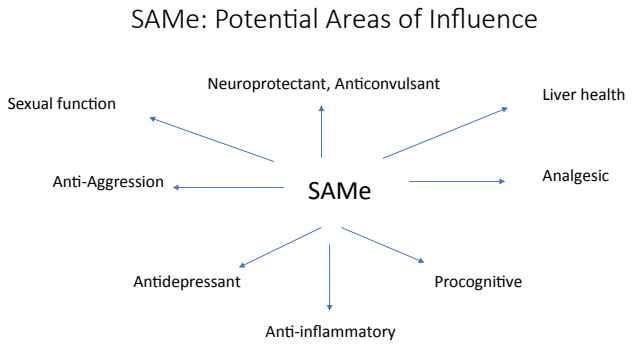

Fig. 1. Schematic summary of potential areas of influence of S-adenosyl-L-methionine (SAMe).

2.3. Anti-inflammation/immuno-modulation actions

Different mechanisms of action have been proposed for SAMe, most of which appear relevant to treatment of depression and neurodegenerative diseases. In particular, anti-inflammatory effects have been identified: (1) Modulation of interleukin (IL)-10 (McClain et al., 2002) and IL-6 production via the adenosine (A2A) receptor (Song et al., 2005). (2) An anti-tumor necrosis factor (TNF) effect through inhibition of lipopolysaccharide (LPS)-induced phosphodiesterase 4B2 (PDE4B2) up-regulation and increased cAMP-dependent protein kinase A (PKA) activation (Gobejishvili et al., 2011). (3) Inhibition of proinflammatory mediators by alteration of the binding capacity of methylated Histone to targeted promoter regions (Ara et al., 2008). (4) Regulation of DNA methylation status of inflammatory genes (Pfalzer et al., 2014). (5) Attenuation of oxidative stress and tumour growth factor (TGF)-β-induced fibronectin expression (Yoon et al., 2016); restoration of normal glutathione (GSH)/glutathione disulfide (GSSG) ratio and increasing activity of glutathione peroxidase (GSH-Px), glutathione S-transferase (GST), and superoxide dismutase (SOD) (Li et al., 2017). (6) Blunting activation of nuclear factor (NF) kappa B through resynthesis of inhibitor kappa B alpha and reduction of transactivation of nitric oxide synthase-2 promoter (Majano et al., 2001). (7) Interactions with the eicosanoid system (Gualano et al., 1983).

2.4. Adverse effects

SAMe is generally well tolerated. The most common adverse effects of SAMe include mild gastrointestinal symptoms: nausea, diarrhea, loose bowels, abdominal discomfort, and rarely, vomiting (Sharma et al., 2017). Other reported side effects include sweating and dizziness (Deligiannidis and Freeman, 2014). Irritability and anxiety may occasionally occur (Bottiglieri, 2013). SAMe has been reported to induce euphoria or mania in patients with bipolar disorder (Mischoulon and Fava, 2002). It may lead to insomnia if taken in the afternoon after 16:00. Compared with other antidepressants, SAMe has rarely caused sexual dysfunction, weight gain and cognitive or memory dysfunction in dementia, Alzheimer's Disease (AD) and traumatic brain injury (Sharma et al., 2017). SAMe can ameliorate abnormal liver function secondary to alcohol abuse, medications, infection, and other causes (Bottiglieri, 2013). SAMe is unlikely to be life-threatening in overdose (Sharma et al., 2017).

2.5. Recommendations

SAMe is a promising natural antidepressant, with growing evidence of efficacy and safety, particularly in MDD (Sharma et al., 2017), and possibly dysthymia (Salmaggi et al., 1993). Larger controlled studies are needed, however, to more conclusively establish SAMe's role in the psychopharmacological armamentarium, both as monotherapy and as augmentation. Oral doses between 400 and 1600 mg/day are common, but some patients may require even higher doses, in the range of 3000–4000 mg/day, which appear to be safe. SAMe is best absorbed when taken at least 20 min before breakfast or lunch (Bottiglieri, 2013). It should also be kept in a sealed box or blister packs to preserve potency and prevent rapid oxidation from exposure to air. Finally, SAMe should be used preferably under the supervision of medical practitioners rather than as self-medication, particularly for depressive disorders that, when inadequately managed, can compromise the patient's overall function and safety. Key information about SAMe is summarized in Table 1.

3. Cannabidiol (CBD) and other marijuana derivatives

3.1. Clinical indications and evidence

Even though cannabis (marijuana) is a Schedule 1 drug in the United States, and, under the Controlled Substances Act (CSA), has been determined to have no accepted medical use, scientific evidence for the role of endocannabinoids in myriad diseases is emerging. The endocannabinoid system (ECS) has received burgeoning attention in the last 25 years for its potential role in central nervous system development, plasticity, and response to insult (Lu and Mackie, 2016). A growing understanding of the widespread impact of the ECS has generated interest in cannabis' medicinal potential and challenged the CSA's classification of cannabis as a Schedule 1 drug. For example, Nabiximols (Sativex), an aerosolized mist for oral administration containing a 1:1 ratio of CBD:tetrahydrocannabinol (THC), has been approved for multiple sclerosis pain in Canada since 2005. Numerous clinical trials show CBD to be effective for certain childhood epilepsies, and an oral CBD solution containing sesame oil (Epidiolex) was approved by the US Food and Drug Administration (FDA) in June 2018 as a treatment for Lennox-Gastaut syndrome and Dravet syndrome (Premoli et al., 2019). As potential uses of cannabis in the treatment of neurological and psychiatric illnesses evolve, it is critical to develop a cogent understanding of the neurobiological effects of both endogenous and exogenous cannabinoids.

The efficacy of THC or CBD in the treatment of mood disorders is not very well supported, and in fact, psychiatric disorders can often be a contraindication for cannabis use. Research has frequently found that cannabis use is associated with an increased risk for depression and anxiety (Danielsson et al., 2016). Likewise, there is evidence of psychotic symptoms and negative cognitive effects developing with cannabinoid use, particularly THC (Krebs et al., 2019; Morgan et al., 2018). However, the causal relationship between cannabis use and certain mood disorders is not well defined. Nonetheless, factors to consider when treating patients with cannabis for mental illness, as opposed to CBD, include the amount of cannabis one is using, the patient's family psychiatric history, any other substances that the patient may be using, and the patient's motive for choosing cannabis as a part of the treatment plan. These nuances have been suggested to be relevant to the efficacy of cannabis use for mental illnesses (Wycoff et al., 2018), and should be carefully considered when deciding upon CBD treatment.

General areas of influence of CBD are illustrated in Fig. 2.

3.2. Dosing and delivery methods

The optimal method of consuming CBD and the appropriate dose are difficult to define because of a wide variety of factors. For example, the ratio of THC to CBD varies greatly depending on what many refer to as the "strain", or the chemical variety of cannabis. Each chemical variety has differing proportions of THC, CBD, and terpenoids, which broadly describe cannabis' psychoactive effects (THC), anxiolytic effects (CBD), and sedative or analgesic effects (terpenoids) (MacCallum and Russo, 2018). Cannabis has therefore been classified based on its ratio of THC:CBD, such that THC-dominant chemical varieties are Type I, equivalent THC:CBD chemical varieties are Type II, and CBD-dominant varieties are Type III. When treating patients with CBD, it is therefore necessary for physicians to consider the chemical variety of cannabis they are choosing.

There is also a wide selection of methods used to ingest both THC and CBD. The way a patient consumes cannabis has a direct effect on the bioavailability of these components. Certain factors, such as the temperature of decarboxylation, depth of inhalation, duration of breath-holding or recent meals all affect the absorption of cannabis, which can vary from 20 to 30% orally, and 10 to 60% with inhalation (Huestis, 2007). Thus, it is important for physicians to weigh the benefits of each of the numerous methods to ingest CBD. For example, while topical application of CBD may be an effective analgesic for localized symptoms, it would have little effect on anxiety. Alternatively, for patients with respiratory symptoms (bronchitis, cough, increased risk for lung cancer, etc.), oral solutions such as edible CBD (infused in honey, for example) or CBD oils (tinctures) would be a better choice

Table 1
Summary of characteristics of SAMe, CBD, and kratom.

Compound	Indications	Efficacy	Doses Used	Delivery Systems	Mechanisms, Anti-inflammatory, and Immunomodulatory Actions	Adverse effects	Recommendations for Clinical Practice
SAMe	(1) Depression (MDD or in context of medical conditions) (2) Cognitive impairment of Dementia (3) Sexual dysfunction (4) Intrahepatic cholestasis in pregnancy (5) Chronic pain (6) Epilepsy	(1) Most supported in depressive disorders, either as monotherapy or as adjunctive therapy	200–4000 mg/day	(1) Oral (2) Intramuscular (3) Intravenous	(1) Modulation of IL-10, IL-6 (2) Anti-TNF effect (3) Inhibition of proinflammatory mediators via histone methylation (4) Regulation of DNA methylation of inflammatory genes (5) Attenuation of oxidative stress and fibronectin expression; glutathione-related mechanisms (6) Blunting of NF kappa B activation (7) Interaction with eicosanoid system	Nausea, diarrhea, loose bowels, abdominal discomfort, vomiting, sweating, dizziness, irritability, anxiety, euphoria or mania in bipolar disorder, insomnia.	Best supported for depression. Begin dosing at 400 mg/day and increase over a few days or weeks to 1600 mg/day, but can go to 3000–4000 mg/day if needed and tolerated.
CBD and cannabis derivatives	(1) Nabiximols (Sativex; CBD:THC = 1:1) for multiple sclerosis pain (2) Oral CBD solution (Epidiolex) for Lennox-Gastaut syndrome and Dravet syndrome (3) Limited evidence on psychiatric disorders	(1) Nabiximols approved in Canada for multiple sclerosis pain (2) Epidiolex approved in the USA for childhood epilepsies (3) CBD is non-intoxicating, reported effects include analgesic, anti-inflammatory, anxiolytic, antipsychotic, anticonvulsant, neuroprotectant	Depends on chemical variety and composition, ratios of THC, CBD, terpenoids	(1) Topical (analgesia) (2) Oral/edible (3) Mist (4) Inhaled (5) Smoked	CBD: (1) Reduction of iNOS, IL-1β, IL-17, IFN-γ, NO; (2) Up-regulation of Wnt/β-catenin pathway (3) attenuation of oxidative stress (4) diminution of mitochondrial dysfunction and reactive oxygen species (5) Downregulation of CCL2 and CCL5 (6) Reduction of FAAH activity (7) increase of anti inflammatory anandamide (8) Suppression of pro-inflammatory Th17-related transcription (9) T cell exhaustion (10) IFN-dependent anti-proliferation (11) inhibition of antigen presentation; (12) antioxidant pathways (13) Interaction with A2A and 5HT1A receptors *CBD vs THC*: (1) CBD reduces NF-κB activity, up-regulates Signal transducer and activator of STAT3 (2) CBD is an agonist for various receptors associated with psychiatric disorders (3) THC acts upon CB1 and CB2 receptors (4) CBD *and* THC decrease production and release of IL-1β, IL-6, IFNβ	Drowsiness, dizziness, dry mouth, cough (when smoked), nausea, and cognitive effects, precipitation or worsening of depression, anxiety, psychotic symptoms.	Potential use in anxiety, depression, or substance use disorders. Avoid as first line treatment in view of limited evidence and potential adverse effects, and always use with caution. Begin with low doses, monitor for side effects, and risk of abuse if patient has prior history of substance abuse.

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Table 1 (*continued*)

Compound	Indications	Efficacy	Doses Used	Delivery Systems	Mechanisms, Anti-inflammatory, and Immunomodulatory Actions	Adverse effects	Recommendations for Clinical Practice
Kratom	(1) Hallucinogenic properties (2) Alleviation of fatigue, withdrawal symptoms from addictive drugs, fever gastrointestinal symptoms (3) Smaller doses may produce stimulant-like effects (increased energy, sociability, alertness), (4) Higher doses may produce opioid-like effects (sedation, pleasure, decreased pain) (5) Other potential indications: anxiety attention deficit disorders (ADD)	Very limited evidence to support clinical use	(1) May vary based on preparation (2) Mitragynine is hallucinogenic, produces stimulant-like effects (1–5 g of raw leaves) and opioid-like effects (5–15 g of leaves	(1) Smoked (2) Chewed (3) Juiced (4) Brewed (5) Ingested as pill, capsule, extract, powder	(1) Mitragynine inhibits COX-2 mRNA and protein expression and prostaglandin E2 (PGE2) formation; pro-inflammatory mediator release inhibition and vascular permeability; affinity for mu-, kappa-, and delta- receptors	(1) Dysregulation of PRL, TSH, TST, LH, FSH (2) Symptoms include loss of libido, infertility, amenorrhea, oligomenorrhea, headache, vision loss (3) Other adverse effects include hypertension, nausea, constipation, confusion, hallucinations, seizures, sedation, withdrawal (cravings, anxiety, 'dread', restlessness, sweating, itching) (4) At least 44 deaths associated with kratom use between 2011 and 2017	Avoid kratom in any patients with history of substance use disorders, particularly opioids. Assess for risk of abuse. Consider effects of withdrawal. Monitor levels of PRL, TSH, TST, LH, and FSH.

Abbreviations

5HT1A: serotonin 1A; A2A: adenosine A2A; CB: cannabinoid; CBD: cannabidiol; CCL2: chemokine (C–C motif) ligand 2; CCL5: chemokine (C–C motif) ligand 5; COX: cyclooxygenase; FAAH: fatty acid aminohydrolase; FSH: follicle stimulating hormone; IFN: interferon; IL: interleukin; iNOS: nitric oxide synthase; LH: luteinizing hormone; MDD: major depressive disorder; NF: nuclear factor; PGE2: prostaglandin E2; PRL: prolactin; STAT3: signal transducer and activator of transcription 3; Th17: T-helper cell 17; THC: tetrahydrocannabinol; TNF-tumour necrosis factor; TSH: thyroid stimulating hormone; TST: testosterone; Wnt: wingless-Int.

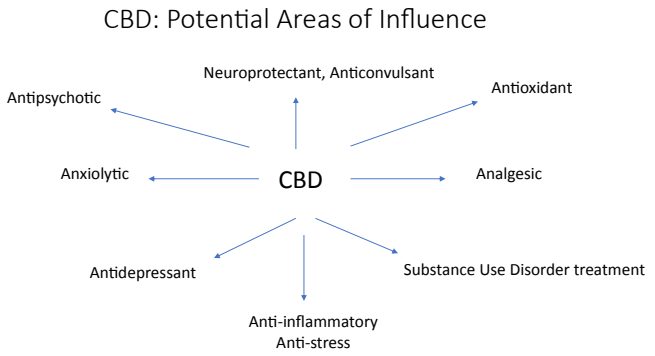

Fig. 2. Schematic summary of potential areas of influence of Cannabidiol (CBD).

(MacCallum and Russo, 2018). Ultimately, the appropriate consumption method should be determined on a case-by-case basis. Patient history, contraindications, a thorough discussion of the pros and cons of cannabis-based medicine, and comfort with CBD on the part of the clinician and patient should be considered.

3.3. Anti-inflammation/immuno-modulation actions

Anti-inflammatory properties of CBD have been well documented by several studies through various mechanisms, especially via: (1) Reduction of nitric oxide synthase (iNOS), IL-1β, IL-17, interferon (IFN)-γ, nitric oxide (NO), and up-regulation of wingless-Int (Wnt)/β-catenin pathway through activation of peroxisome proliferator-activated receptor γ (PPARγ) and attenuation of oxidative stress; decrease of mitochondrial dysfunction and reactive oxygen species generation in mouse models (Esposito et al., 2007; Giacoppo et al., 2017; Ribeiro et al., 2011; Sonego et al., 2018; Vallee et al., 2017). (2) Down-regulation of expression of chemokines (CCL2 and CCL5) in a TMEV-induced demyelinating disease (TMEV-IDD) model (Mecha et al., 2013). (3) Decrease of fatty acid aminohydrolase (FAAH) activity, thereby increasing production of anandamide, an anti-inflammatory endocannabinoid (Zurier and Burstein, 2016). (4) Suppression of pro-inflammatory Th17-related transcription; promotion of T cell exhaustion; enhancement of IFN-dependent anti-proliferation; inhibition of antigen presentation; and induction of antioxidant pathways to resolve inflammation in autoimmune T cells (Kozela et al., 2016). (5) Interaction with A2A and 5HT1A receptors (Magen et al., 2009, 2010).

Interestingly, THC and CBD display partially overlapping but different anti-inflammatory mechanisms. CBD reduces activity of the NF-κB pathway and up-regulates the activation of the signal transducer and activator of transcription factor (STAT3) but THC does not. Both CBD and THC decrease production and release of pro-inflammatory cytokines, including IL-1β, IL-6, and IFNβ, from LPS-activated microglial cells (Kozela et al., 2010). Further, THC acts upon CB_1 and CB_2 receptors, whereas CBD is an agonist for a wide variety of receptor targets that play distinct roles in psychiatric disorders (Zlebnik and Cheer, 2016). When acting upon these diverse receptor systems, CBD is a non-intoxicating agent that produces analgesic, anti-inflammatory, anxiolytic, and antipsychotic effects with added benefits as an anticonvulsant and neuroprotectant (MacCallum and Russo, 2018).

3.4. Adverse effects

Common side effects of CBD may include drowsiness, dizziness, dry mouth, cough (when smoked), nausea, and cognitive effects (MacCallum and Russo, 2018). Providers must also consider that there is currently no serum assay that can accurately measure impairment due to cannabis products, and patients should not consume cannabis-based medicine (especially THC-predominant ones) within eight hours of operating heavy equipment (MacCallum and Russo, 2018). The increasing legalization of marijuana and related products will require accurate measures of intoxication that can be used in the field, e.g. by police or firefighters in cases of accidents where cannabis-related intoxication may be suspected.

3.5. Recommendations

Mechanistic evidence suggests the possibility that CBD could potentially serve in the treatment of psychiatric disorders including anxiety, depression, or substance use disorders. But because of the lack of evidence from randomized clinical trials, and concerns over potential serious adverse effects (Krebs et al., 2019) such products should certainly not be used as a first line treatment, and when used in limited cases (e.g. patients who have not responded to standard therapies and/or could not tolerate side effects), caution should always be observed. As with all new and unproven treatment methods, a detailed conversation of the pros and cons of CBD should occur between providers and patients, and those who try CBD should start with low doses and titrate to larger doses as needed (MacCallum and Russo, 2018). Included in the treatment plan should also be regular check-in appointments and potentially a log for patients to record side effects. Finally, while CBD appears to have low abuse potential, providers should carefully consider the risks of abuse (e.g., if the patient has a history of abuse of cannabis or other recreational drugs) when recommending it as a treatment (Katsidoni et al., 2013). Key information about CBD is summarized in Table 1.

4. Kratom

4.1. Clinical indications and evidence

Kratom, a tropical tree native to Africa and Southeast Asia, has recently received attention for its potential as an alternative treatment for certain psychiatric disorders (NIDA, 2018). Kratom (*Mitragyna speciosa*) is a perennial herb classified as a member of the coffee family (Babu et al., 2008; Warner et al., 2016). Kratom should not be confused with *Salvia divinorum*, a member of the mint family also recognized for having strong hallucinogenic properties and opioid-like effects (Babu et al., 2008; Tidgewell et al., 2004).

Traditional uses of kratom differ throughout the world. In Southeast Asia, where the plant is indigenous, kratom has traditionally been used to alleviate fatigue and improve farmland productivity, similarly to the chewing of coca leaves in South American countries (Cinosi et al., 2015). However, kratom's potential as a treatment for psychiatric disorders may have originated in Thailand, where for many decades it has been used to treat withdrawal symptoms from addictive drugs (Warner et al., 2016). As interest has spread to Western countries, the plant has received attention for its psychoactive abilities. As previously mentioned, traditional indications of kratom have included withdrawal symptom management, energy enhancement, and combating fever or gastrointestinal symptoms (Singh et al., 2016). More recently, kratom is being marketed as a "legal high" in the United States (Swogger and Walsh, 2018), where it is currently used as an unscheduled psychoactive and is thought to cause effects similar to those of both opioids and stimulants (NIDA, 2018).

Alongside its stimulant- and opioid-like effects, kratom may have the potential to treat anxiety and attention deficit disorders (ADD) through activation of α-2 adrenergic receptors (White, 2018). In the treatment of ADD, lower doses may increase energy and motivation. When considering anxiety, kratom is known to produce sedation, but the extent to which kratom can be an anxiolytic without producing unwanted drowsiness has yet to be studied. In 2017, a large study indicated that 76% of U.S. users of kratom reported using it to relieve negative moods, including anxiety, depression, and posttraumatic stress (Grundmann, 2017).

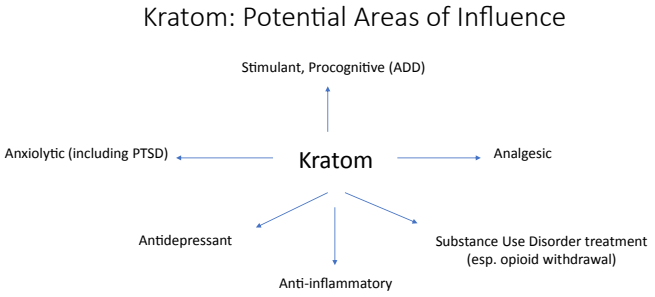

Fig. 3. Schematic summary of potential areas of influence of kratom.

Kratom may also be beneficial as a harm-reducing substitute for other opioids (Swogger and Walsh, 2018). A recent survey of 500 individuals participating in a 12-step program for polysubstance use disorders inquired about kratom use. Results showed that 21% used kratom at least once in their life, and 10% in the past 12 months. Kratom usage patterns included: 1) As a "safe" heroin alternative to help individuals abstain, including as-needed use when no opioids were available; 2) Casual 1–2 time use; 3) Long-term replacement for opioids, including IV heroin use (Smith and Lawson, 2017).

General areas of influence of kratom are illustrated in Fig. 3.

4.2. Dosing and delivery methods

Modes of consuming kratom differ, depending on geographical location. For example, in much of Southeast Asia the leaves are smoked, chewed, or brewed as an herbal solution. In Thailand the leaves are chewed, and in Malaysia the leaves are juiced (Singh et al., 2016). Doses are therefore difficult to infer from these modalities of consumption. According to the National Institute on Drug Abuse (NIDA), kratom is easily ordered on the internet. In the US and much of the industrialized world, kratom is usually taken as a pill, capsule, extract, or powder (NIDA, 2018). It can also be smoked or eaten in food.

There is a great variance in the amount of kratom's main active ingredient mitragynine (see Section 4.3 for details) found in different preparations of kratom. This makes accurate dosing difficult. In general, a low to moderate dose is typically defined as 1–5 g of raw leaves, whereas 5–15 g of leaves is considered a higher dose (Warner et al., 2016), with an estimated 17 mg of mitragynine in 20 leaves (Babu et al., 2008). The degree of hallucinogenic and clinical effects depend on the route of administration and actual dose ingested (Babu et al., 2008; see Section 4.3 for details).

Smaller doses of kratom may produce stimulant-like effects (increased energy, sociability, and alertness), and higher doses may produce opioid-like effects (sedation, pleasure, decreased pain) (NIDA, 2018). The threshold doses for these effects and their duration are not well characterized, however (Babu et al., 2008).

4.3. Anti-inflammation/Immuno-modulation Actions

A very few studies have documented anti-inflammatory effects from kratom (White, 2018). In a cellular study, mitragynine was found to inhibit COX-2 mRNA and protein expression as well as prostaglandin E2 (PGE2) formation revealing their role in suppression of inflammation (Hassan et al., 2013). Similarly, in animal studies, kratom has demonstrated pro-inflammatory mediator release inhibition and vascular permeability effects (Dongmo et al., 2003; Fluyau and Revadigar, 2017; Shaik Mossadeq et al., 2009). These limited studies suggest that kratom may be useful for treating inflammatory conditions prevalent in psychiatric disorders (Utar et al., 2011).

Mitragynine is also responsible for opioid-like effects with affinity for both supraspinal opioid mu-, kappa-, and delta- receptors. Activation of the mu- receptor mediates the analgesic, euphoric, and anti-withdrawal effects (Thongpradichote et al., 1998).

4.4. Adverse effects

Reported adverse effects of kratom use include dysregulation of prolactin (PRL), thyroid stimulating hormone (TSH), testosterone (TST), luteinizing hormone (LH), and follicle stimulating hormone (FSH). Symptoms of dysregulation of these hormones may include loss of libido, infertility, amenorrhea, oligomenorrhea, headaches, or vision loss (LaBryer et al., 2018). Other adverse pharmacological effects of kratom use may include hypertension, nausea, constipation, sedation, confusion, hallucinations, and seizures (White, 2018).

The US Food and Drug Administration (FDA) has recently issued several warnings, citing at least 44 deaths associated with kratom use between 2011 and 2017 (NIDA, 2018), both by itself and mixed with other substances such as opioids. Withdrawal symptoms from kratom are not well understood, but one case report cited cravings, anxiety, sensation of 'dread', restlessness, sweating, and itching (McWhirter and Morris, 2010). The potential for abuse, withdrawal, severe adverse events, and variable psychotropic effects make kratom an alternative treatment that requires very close supervision when used. In this regard, it is relevant to note that urine toxicology screens do not detect the presence of mitragynine and there is no method for its detection in human blood (Tidgewell et al., 2004; Warner et al., 2016). If kratom is to be considered as a treatment for psychiatric illnesses, it is paramount that providers evaluate the exact mechanisms, risks, and benefits of kratom in accordance with their patient's individual needs and medical history to make a cautious decision.

4.5. Recommendations

There are several factors for practitioners to consider before prescribing kratom for the treatment of psychiatric disorders. Primarily, physicians should avoid kratom in any patients who have had previous substance use disorders, particularly those involving opioids. Kratom is an addictive substance, and the patient's entire medical history should therefore be evaluated to ensure that the risk of abuse is documented (LaBryer et al., 2018). Physicians should also weigh the risks of withdrawal versus the benefits of using kratom, and carefully monitor for any withdrawal symptoms. Regular blood tests to monitor the levels of PRL, TSH, TST, LH, and FSH should be obtained. Ultimately, most of the research on kratom use in mood disorders involves cross-sectional or case reports. Therefore, there is a significant need for well-controlled, prospective studies to gain a more robust understanding of the benefits and harms of kratom use in mental health. Key information about kratom is summarized in Table 1.

5. Conclusions

We have reviewed three natural products with known and potential applications in mood disorders. Of the three, SAMe is the one that has received the most clinical trial-based support and is now more widely used in clinical practices, often by psychiatrists who are comfortable with natural products. With kratom and CBD, the jury is still out, and more research will be needed to better characterize their efficacy, and perhaps, more importantly, their safety, for use in regular psychiatric practice. Mechanistically there is still much to learn about these remedies, but the evidence so far shows their activities to be varied and complex. Their interaction with the immune and inflammatory system is supported but requires more evidence to better characterize their full range of action in the human organism and particularly in the brain.

For the time being, we can recommend SAMe with relative confidence, given the large body of evidence that generally supports efficacy, and more strongly supports safety. Kratom and CBD, while they may eventually find use in clinical practice, need to be managed very carefully. We would not recommend them in individuals with severe

mood disorders, except possibly as adjuncts in people who have already exhausted many standard options and are not considered at risk of misusing or abusing these substances. In people with milder illness who have little to lose by trying one of these remedies, judicious use may be beneficial in carefully selected cases. With kratom and CBD, extreme caution should be exercised in patients with histories of substance use disorders. Finally, when treating psychiatric disorders, these medicines should always be used under the direction of a licensed clinician, and preferably one with expertise on natural remedies.

Declaration of Competing Interest

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The other authors report no significant conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2019.07.013.

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