Supplements and Natural Remedies for Depression

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Case Vignette

Bill was a 35-year-old married white male with no significant history of depression, who presented in a psychiatrist's office at the recommendation of his primary care physician. Bill had been feeling depressed for a few months and had reluctantly accepted a trial of fluoxetine 20 mg/day from his primary care physician (PCP). When his depression improved only partially after 3 months, and the PCP's attempt to increase the dose of the fluoxetine led to side effects (headaches and sexual dysfunction), Bill agreed to see a psychiatrist when the PCP explained that untreated depression could become more severe over time and that depression is best managed by specialists.

The psychiatrist diagnosed Bill with mild major depressive disorder and recommended changing to another standard antidepressant. Bill was reluctant, because historically he had been prone to side effects from different kinds of medications. The psychiatrist discussed the possibility of trying an over-the-counter natural product before further consideration of a registered antidepressant. He explained to Bill that many people benefit from these therapies, which are often better tolerated, though less well-characterized compared to FDA-approved drugs. Bill liked the idea and agreed to try a natural product.

They reviewed a few options. St John's wort was ruled out because of concerns over adverse interactions with fluoxetine, which Bill wanted to keep taking for the time being. Omega-3 fatty acids and s-adenosyl methionine (SAMe) were then considered, in view of their safety in combination with standard antidepressants. Bill agreed to try an omega-3 preparation. The psychiatrist recommended he start at 1000 mg/day of a preparation consisting of at least 60% eicosapentaenoic acid (EPA), and Bill purchased one at his local pharmacy. Per the psychiatrist's instructions, he began taking the supplement and returned 1 month later for follow up, reporting no improvement. An attempt to increase the dose to 2000 mg/day did not produce any additional benefit after another month.

The psychiatrist discontinued the omega-3 and started Bill on S-adenosyl-L-methionine (SAMe) at 800 mg daily. When Bill returned 4 weeks later, he reported that he was feeling better. His mood was not as down, his sleep had improved slightly, and his concentration was better, though he still felt somewhat scattered. He reported no side effects. In view of the promising but incomplete response, the psychiatrist recommended increasing the SAMe to the more accepted therapeutic dose of 1600 mg/day for another month. When Bill returned 4 weeks later, his depression had completely resolved, with no new side effects.

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Introduction/Definition of Natural Remedies and Related Terms

Natural products have been used for various medical and psychiatric indications for thousands of years. They typically are described and categorized as natural, alternative, or complementary, among other names. Complementary and alternative medicine (CAM) may also refer to interventions such as acupuncture, meditation, and other treatments that do not involve medications. Natural remedies are marketed as over-the-counter dietary supplements for health benefits and are not generally approved by the US Food and Drug Administration (FDA) [1]. In this chapter, the terms "natural," "nutraceutical," "complementary," and "alternative" will be used when describing the specific products covered. Briefly, a "dietary supplement," as defined by the Dietary Supplement Health and Education Act of 1994 (DSHEA), refers to a product intended to supplement diet that contains vitamins, minerals, amino acids, herbs, or other natural substances used to supplement the diet by increasing their total dietary intake [2]. These can take the form of a concentrate, metabolite, constituent, extract, or combination of the above, and not represented as a food or as a sole item of a meal/diet. A "nutraceutical" is defined as a foodstuff (fortified food or dietary supplement) that provides some health benefit. The remedies discussed in this chapter could be defined by any of these terms.

History and Socioeconomic Perspectives

Natural remedies have become an integral part of American culture, representing a growing component of healthcare and self-care, and psychiatric disorders such as depression constitute one of the leading families of disorders that are treated with alternative therapies. Despite the more than 40 available FDA-approved antidepressants, up to half of depressed patients who receive pharmacological treatment will fail to respond; and among those who do respond, many will have depressive recurrence [3]. Medication-related side effects may also dampen the success of pharmacological treatment by leading to poor adherence and early discontinuation [4]. Natural remedies could therefore prove to be a valuable addition to the clinical armamentarium, given their reported effectiveness, good acceptability, and tolerability [5].

Despite the popularity and promise of nutraceuticals, there are many concerns about their growing use. First, nutraceutical agents are not as tightly regulated as medications approved by the FDA for an illness indication [1]. Manufacturers may therefore make carefully worded statements about safety and effectiveness, by avoiding claims about prevention or treatment of specific illnesses. Second, the relative concentration of active ingredients may vary between different preparations of the same remedy, which can impact on efficacy and side effects. Third, natural therapies are generally not covered by medical insurance, requiring consumers to pay out of pocket for them. Individuals considering these remedies therefore need to be careful and weigh the costs and benefits of nutraceuticals.

Given these concerns, data from clinical and mechanistic trials can clarify efficacy, safety, and mechanisms of action of these therapies. Likewise, cost-effectiveness studies can help determine whether insurance companies should cover them as a way of containing healthcare utilization, such as inpatient hospitalizations. Unfortunately, large, rigorous, well-designed controlled trials for these nutraceutical products are sorely lacking. The nutraceutical industry does not have the same financial resources as the pharmaceutical industry, which limits their capacity to sponsor research. Even nutraceutical manufacturers who have enough resources to invest in research may be reluctant to do so [1], given the risks involved in putting your product to the test. A clinical trial that supports efficacy of a supplement may not necessarily increase sales enough to justify the cost of the research, but a negative trial showing no advantage over a placebo could significantly decrease sales. For example, in the early 2000s, three large-scale clinical trials on St. John's wort (SJW) suggested no significant advantage for SJW over placebo [6–8]. This led to negative publicity for SJW, decreased worldwide sales [9], and, in some cases, the premature termination of funding for studies on SJW [10, 11].

While industrial funding for nutraceutical research remains limited, it is fortunate that the US Government continues to support research on natural remedies. With continued sponsorship by organizations such as the National Center for Complementary and Integrative Health (NCCIH), or by private foundations with minimal conflict of interest, the research produced might prove more trustworthy when compared to industry-funded studies [1].

If the medical profession can use these data to issue more reliable recommendations to the public, the consumer could make better-educated decisions about these therapies. Likewise, quality research and careful safety monitoring could help prevent widespread catastrophic toxic reactions from these agents, as have occurred with cases of liver failure from kava [11], transplant rejection and failure of anti-HIV agents from SJW [12, 13], and sudden death from ephedra [14].

Continued research on nutraceuticals, as well as other complementary therapies depicted in this book, remains of paramount importance, both scientifically and as consumer protection. It is hoped that scientists will be able to continue to rigorously study the benefits and liabilities of natural therapies.

The remainder of this chapter will focus on selected natural remedies, evidence for efficacy, proposed mechanisms of action, and known or potential adverse effects.

New Advances and Research Support

St. John's Wort

St John's wort (SJW; *Hypericum perforatum* L.) is an herbal remedy with great worldwide popularity. It is one of the better studied natural remedies for depression, with about 40 published clinical trials [15]. The efficacy of SJW monotherapy for depression has been compared to tricyclic antidepressants (TCAs) and more recently against selective serotonin reuptake inhibitors (SSRIs). As the body of evidence has grown, various systematic reviews and meta-analyses have emerged, examining these studies as a whole [15, 16]. In sum, these syntheses support SJW's antidepressant effect as greater than placebo's, and comparable to that of low-dose TCAs and therapeutic doses of SSRIs, though there is disagreement among individual studies. SJW also has shown good tolerability and lower discontinuation rates than registered antidepressants, which may in part explain its popularity [15]. The published studies have some limitations, including a focus on less severe forms of depression, limited data on adverse effects, and shorter treatment periods than typically established for antidepressants.

SJW is thought to function via effects of hypericin, pseudohypericin, and hyperforin [17, 18]. These may interact with the hypothalamic-pituitary-adrenal axis to reduce cytokine production and also have some serotonergic activity. SJW also has some mild MAOI activity [19]. While no special diet is required for people taking SJW, it should not be combined with SSRIs, due to the risk of serotonin syndrome (hypertension, hyperthermia, flushing, hyperreflexia, dizziness, disorientation, and myoclonus) [12]. SJW has other documented interactions via induction of cytochrome P (CYP)-3A4 that result in reduced clinical effects of warfarin, cyclosporin, oral contraceptives, theophylline, fenprocoumon, digoxin, indinavir, zolpidem, irinotecan, olanzapine, and probably others [20]. Caution is therefore necessary with patients taking multiple medications, since some severe reactions, such as transplant rejection, breakthrough pregnancy, and development of resistant HIV strains, may occur. Apart from these concerns, SJW is generally safe and well tolerated. Typical side effects include dry mouth, dizziness, and constipation [20]. Phototoxicity or increased sensitivity to sunlight may occur; for which reason, we advise that those taking SJW should be careful when going to the beach or on a hike. Proper protection such as sunscreen and hats should be used. There have been cases of cycling to mania occurring in patients with bipolar disorder who self-medicate with SJW for the depressive phase of their illness [21]. For this reason, these individuals should use SJW in combination with a mood stabilizer and under clinician supervision. Regarding safety in pregnancy, preliminary reports suggest no significant risks, but caution is advised nonetheless [22].

Overall, the body of evidence is generally supportive of SJW as a natural antidepressant, despite some inconsistencies between studies. Recommended doses are reported between 300 and 1800 mg/day, usually divided in a twice or three times daily basis. Practitioners should be aware that different preparations may vary with regard to amount of active ingredients present, and this can result in variations in efficacy between different brands.

S-Adenosyl-L-Methionine (SAMe)

S-adenosyl-L-methionine (SAMe) is another natural antidepressant that has been used extensively in Europe for decades but has attained popularity in the USA only since the late 1990s [23, 24]. SAMe is produced by all living beings and functions as a methyl donor in many important physiologic reactions, most notably neurotransmitter synthesis. SAMe comprises part of the one-carbon metabolic cycle, which involves folic acid and vitamin B12, among other factors [25]. The synthesis of SAMe depends in part on the enzyme methylenetetrahydrofolate reductase (MTHFR). Certain genetic polymorphisms can render this enzyme less functional and negatively impact on the one-carbon cycle balance [26]. Therefore, administration of SAMe could potentially bypass the need for MTHFR in deficient individuals who become depressed. It could also help non-deficient individuals by simply boosting production of the key neurotransmitters such as serotonin, dopamine, and others.

Like SJW, SAMe is a well-studied natural antidepressant. About 50 clinical trials have been published, including oral, intramuscular, and intravenous administration schedules, with doses ranging from 200 to 3200 mg/day [23, 24, 27]. There has been one major meta-analysis by Hardy and colleagues [23], generally supporting SAMe as more effective than placebo and about equivalent to tricyclic antidepressants. A more recent small meta-analysis of adjunctive SAMe and other therapies also supports SAMe [28]. A recent systematic review [24] points out that relatively few new SAMe studies have emerged since 2002, which means the Hardy meta-analysis remains the most comprehensive. Among the more recent studies include one comparison between SAMe and escitalopram [29], which remains the sole comparison between SAMe and an SSRI to date. This study recruited 189 patients and randomized them for 12 weeks to either SAMe (1600–3200 mg/day), escitalopram (10–20 mg/day), or placebo. The study was limited by a high placebo response rate that resulted in equivalence between the three treatment arms, though improvement was significant for each group. Ancillary analyses suggested that men may respond to SAMe better than women [30].

One of the appealing qualities of SAMe is that it appears to have few interactions with other drugs, which makes it

safe to combine with standard antidepressants. There have been thus far combination studies with TCAs, SSRIs, and SNRIs. For example, Alpert and colleagues [31] examined SAMe augmentation in a small sample of 30 SSRI nonresponders. Subjects received open-label SAMe 800–1600 mg/day with overall response rates of 50% and remission rates of 43% and minimal complaints of adverse effects. Papakostas and colleagues [32] pursued this line of investigation with a double-blind controlled study of SAMe augmentation in SSRI and SNRI nonresponders. After 6 weeks of treatment with SAMe 800 mg twice daily or placebo, results showed a significant advantage for SAMe over placebo, with response rates of 36.1% vs. 17.6%, respectively, and remission rates of 25.8% vs. 11.7%, respectively.

Overall, the results for SAMe are encouraging at 400–3200 mg/day, though some patients may need higher doses. SAMe is generally well tolerated and safe. It is recommended to use forms that come in blister packs, since those are less likely to decompose on the shelf [33]. The most common side effect we have observed in our patients is gastrointestinal upset [29, 32]. Other reported side effects include insomnia, anorexia, dry mouth, sweating, dizziness, and anxiety. There have been cases of mania and hypomania occurring in patients with bipolar depression who try SAMe [34, 35]. Regarding pregnancy, it is known that pregnancy is associated with decreased SAMe and methylation activity. A meta-analysis examining studies of pregnant women with intrahepatic cholestasis suggested benefit of SAMe [36]. While it is likely safe for a pregnant woman with depression, better safety data are needed before firm recommendations can be made. A final caveat about SAMe is that it is among the more expensive of these natural products for depression, costing from $0.75 to 1.25 for a 400 mg tablet. Many consumers therefore need to discuss the cost-benefit issues with their clinician prior to embarking on a course of SAMe.

Omega-3 Fatty Acids

The omega-3 fatty acids are a family of long-chain polyunsaturated fatty acids. They are found primarily in fish oil and other marine sources [33]. The two main omega-3s of interest in psychiatry are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are considered to be the most psychotropically active [33]. Since the late 1990s, they have been extensively studied as potential psychotropic agents. They are thought to function in various ways including G-protein signaling inhibition, neuronal membrane stabilization, anti-inflammatory effects, and other activities [37].

At this time, there are more than 30 published clinical trials examining different omega-3 preparations in depressed populations, and various systematic reviews and meta-analyses, which are generally supportive of omega-3 preparations as effective for treatment of depression [33, 37, 38]. Most of these studies used adjunctive omega-3 in samples with limited response to standard antidepressants, but there are also several monotherapy studies of omega-3. Most of these studies tend to use either EPA as the sole omega-3 or combinations of EPA and DHA. Doses used vary, but typically fall between 1 and 2 g/day in most studies. A recent meta-analysis by Sublette and colleagues [38] found that preparations with at least 60% EPA relative to DHA appear to be the most effective.

There is limited evidence for DHA [39–42]. Mischoulon and colleagues found benefit in one double-blind, uncontrolled dose-finding study comparing three regimens of DHA monotherapy, with greatest benefit at 1 g/day and less at 2 g and 4 g/day. A comparative study of EPA and DHA found less benefit for DHA, but that EPA may be more effective in people who are overweight and/or have elevated inflammation [42, 43]. Marangell and colleagues found no benefit for DHA at 2 g/day [40].

There are various other potential indications for omega-3s, though studies are limited. These include postpartum depression [44, 45] and bipolar disorder [46, 47]. In the latter, most of the benefit from omega-3 may be in the depressed phase rather than mania [48]. Benefits have been suggested in psychotic disorders [49], though perhaps omega-3s may work best at prevention rather than treatment of psychosis. Certain characteristics of borderline personality disorder may be alleviated by omega-3 [50]. Recent evidence has suggested benefit in children and adolescents with depression [51] and with attention deficit disorders [52]. Thus far, there is little evidence in dementia [53]. There is a study in progress examining preventive effects of omega-3 and vitamin D for depression in older people [54].

The data for omega-3s are overall difficult to interpret. While the meta-analyses are, as previously mentioned, generally supportive, they also reveal disagreement between different clinical trials, largely due to heterogeneity among studies with regard to omega-3 preparations, doses, and study design [33, 38, 48, 55–58]. Likewise, there are no published head-to-head studies with different preparations.

Given the current knowledge base, the following recommendations can be made. For unipolar depression, 1–2 g/day of an EPA/DHA combination, with ≥60% EPA [38], may represent the best starting regimen. While studies for bipolar disorder have used higher doses (6–10 g/day), caution should be taken because there have been cases of cycling. Other side effects include stomach upset and fishy taste, which are less common today with improved manufacturing standards. Likewise, early concerns about risk of bleeding may have been exaggerated [59], but caution is still advised [60]. Regarding pregnant women, omega-3s are critical to the development of the infant brain, and pregnancy depletes omega-3 in the mother [61]. There is therefore reason to

postulate benefit from omega-3 to expectant mothers, the fetus, and infants. While fish consumption in pregnancy is now supported [62], we do not know the full ramifications and safe upper limits of omega-3 doses in pregnancy, and therefore caution is advised.

Rhodiola rosea

Rhodiola rosea, commonly referred to as "golden root" or "arctic root," grows at high altitudes in mountainous regions of Europe and Asia [63]. Rhodiola has been used for centuries in traditional medicine of Asia, Scandinavia, and Eastern Europe. While its mechanism of action is not well understood, it is believed to work as an "adaptogen," meaning that it increases resistance to chemical, biological, and physical stressors. It may also stimulate activity of the nervous system and enhance physical and mental performance. Of particular relevance to psychiatry, rhodiola has been suggested to alleviate fatigue, stress, depression, and impotence [63].

Rhodiola has been extensively studied in Russia and Scandinavia for more than 40 years, though most of this research has yet to be translated to English, remaining largely inaccessible for US researchers. Studies that have been translated generally support rhodiola as effective for treating depression. At least four controlled trials demonstrate antidepressant and anxiolytic effects and enhancement of cognition [63, 64]. Other studies have been less encouraging. For example, a comparison of rhodiola 340 mg vs. sertraline 50 mg vs. placebo did not show significant clinical separation between treatments, but rhodiola was better tolerated [65]. Another trial, using doses ranging from 100 to 680 mg/day, did not support efficacy for self-reported anxiety, stress, cognition, and other mood symptoms [65].

Rhodiola contains many chemicals that may have beneficial effects on mood. Rosavins, salidroside, and p-tyrosol are thought to provide the adaptogenic effect [66]. Flavonoids and organic acids serve as antioxidants. Other proposed mechanisms include monoamine and catecholamine modulation, in part via MAO-A and MAO-B inhibition that impacts on levels of serotonin, dopamine, and norepinephrine [67, 68]. Opioid-like effects via induction of opioid biosynthesis and activation of central and peripheral opioid receptors have also been reported [69]. Rhodiola also reduces secretion of corticotrophin-releasing factor (CRF) and thus mediates stress by reversing anxiogenic activity of CRF [70, 71]. Typical commercial preparations of rhodiola are standardized to a minimum 3% rosavins and 0.8% salidroside (naturally occurring at a 3:1 ratio).

Side effects from rhodiola are infrequent and mild. The most common include allergic reactions, irritability, insomnia, fatigue, and unpleasant sensations, especially at high doses. Rhodiola should preferably be taken at least 30 min before meals and early in the day because at night it may interfere with sleep or cause vivid dreams [63]. Rhodiola appears to have few interactions with other drugs, and it has been successfully combined with TCAs, even demonstrating reduction of TCA side effects [63]. However, a recent report of mild serotonin syndrome with paroxetine [72] supports caution about combining rhodiola with standard agents. One report of a study in mice suggests that rhodiola is safe in pregnancy and lactation [73], but human studies are needed to clarify this. There appear to be no data on bipolar cycling, but given its energizing nature, rhodiola should probably be used with caution in this population.

Overall, rhodiola seems like a promising natural agent for treatment of mood disorders, though not as well studied as the previous agents covered so far. The unavailability of translations of many studies hinders a complete assessment of the body of knowledge, and for this reason, more studies are needed to better understand how rhodiola is best applied. Rhodiola's clearest indication seems to be for asthenic or lethargic conditions secondary to intense physical or mental strain [63]. Mechanistically, the demonstrated monoamine modulation is in line with its proposed antidepressant effect. Whether rhodiola should be combined with standard antidepressants remains unclear. In theory, combining rhodiola with SSRIs or SNRIs might diminish side effects such as poor memory, sexual dysfunction, and weight gain, but the case report of serotonin syndrome with paroxetine [72] suggests that caution must be taken with combination therapy. Controlled studies should be pursued.

Vitamin Supplements

Folic Acid

While the link between folic acid deficiency and depression is well known, there have been relatively few studies of folate supplementation for depression [74]. While studies have been generally positive, the body of work is limited by small samples and heterogeneity of folate preparations (e.g., folic acid, leucovorin, etc.). L-methylfolate (5-methyltetrahydrofolate; 5-MTHF), marketed as Deplin, has been a growing part of the psychopharmacology armamentarium [75]. Approved by the FDA for supplementation of or prevention of vitamin deficiency, it has gained popularity as an augmentative agent in depression. Deplin's role as an antidepressant was supported by a multicenter, randomized, double-blind study by Papakostas et al. [75] in which adults 18–65 years with MDD and moderate to severe depression and not responding to SSRI for ≥8 weeks were randomized to augmentation with L-methylfolate 15 mg/day vs. placebo. Results showed that L-methylfolate 15 mg/day produced a greater decrease in depressive symptoms based on several diagnostic instruments than did the placebo.

Other L-methylfolate preparations include Cerefolin, which contains 5.6 mg L-methylfolate (Metafolin), 1 mg of vitamin B12 (cyanocobalamin), 50 mg of vitamin B2 (riboflavin), and 5 mg of vitamin B6 (pyridoxine). Its variant, Cerefolin NAC, includes methylcobalamin 2 mg and N-acetylcysteine (NAC) 600 mg (NAC is discussed in the section on mitochondrial modulators). Like Deplin, Cerefolin and Cerefolin NAC are approved for the treatment or prevention of vitamin deficiencies and available by prescription. They are often used off-label for psychiatric indications, including depression and dementia and their roles in these conditions merit further investigation.

Other Vitamin Supplements

There has been a growing interest in the application of broad spectrum micronutrients, such as EmpowerPlus (EMP) for the treatment of different health problems. EMP contains about 40 trace minerals, vitamins, and inositol. Rucklidge and colleagues have published extensively on EMP or variations thereof in various mental health conditions, with encouraging but mixed results [76–78]. These preparations may have benefits on stress [79, 80], attention deficit disorders in children and adults [81–83], bipolar disorder, obsessive compulsive disorder [84, 85], and cognition [86]. Despite many legal controversies over claims made, most of the lawsuits have been settled in favor of the manufacturer. More systematic research is needed on broad spectrum supplements of this type.

Other mega-vitamin therapies (>200% of RDAs) have also been marketed as a "cure" for many illnesses. However, many preparations that contain fat-soluble vitamins such as vitamin A and D that are stored do in theory carry a risk of hypervitaminosis [87, 88] and should therefore be used with caution.

5-Hydroxytryptophan (5-HTP)

The amino acid 5-HTP, a serotonin precursor, is obtained commercially as an extract from the African plant *Griffonia simplicifolia*. It is produced chemically from the essential amino acid L-tryptophan (L-TRP). L-tryptophan (L-TRP) can also be used for serotonergic boosting, but 5-HTP has the advantage of bypassing conversion of L-TRP into 5-HTP by tryptophan (TRP) hydroxylase, which is the rate-limiting step of the conversion of tryptophan to serotonin [63]. TRP hydroxylase may be inhibited by various disease states and physical or psychological stress. In such cases, L-TRP is converted to kynurenine via tryptophan 2,3-dioxygenase, which decreases L-TRP availability for serotonin production. 5-HTP supplementation can bypass this step, and increase the amount transported across the blood-brain barrier (BBB) for conversion to serotonin [89, 90]. Other key regulators of mood and sleep that have been shown to increase with oral 5-HTP ingestion include melatonin, dopamine, norepinephrine, and beta-endorphin. The L-enantiomer of 5-HTP is the most biologically active form. Proposed indications for 5-HTP include depression, fibromyalgia, insomnia, binge eating disorders, cerebellar ataxia, and headaches [63].

Most of the key trials on 5-HTP were conducted in the 1970s and 1980s, when the serotonin hypothesis of depression was popular [63]. There are about 27 published clinical studies for depression, of which eight were double blind, with four using an active comparator; three involved augmentation with nialamide, clomipramine, or TRP; one study used a crossover relapse prevention design; and one examined a 5-HTP/dopamine agonist combination. Overall, 5-HTP outperformed the placebo in most studies, often with improvement within 2 weeks. Limitations of these studies include small samples, and only six studies showed a statistically significant advantage for 5-HTP over placebo. A Cochrane review suggested that only two studies, both showing superiority over placebo, are truly rigorous enough to merit consideration for a mini-meta-analysis [91].

Two significant events led to a virtual stoppage of 5-HTP research in the 1990s: first, the emergence of prescription selective serotonin reuptake inhibitors (SSRIs) in the late 1980s and, second, outbreaks of about 1500 cases of L-tryptophan-related eosinophilia-myalgia syndrome (EMS) in 1989 and 1990, resulting in at least 38 deaths. The FDA consequently banned tryptophan until further study showed that EMS was due to bacterial fermentation products secondary to inadequate filtration in the manufacturing process. 5-HTP was eventually reinstated on the market with more rigorous manufacturing practices, and current data support its safety [63].

The most common adverse effects associated with 5-HTP are gastrointestinal (nausea, vomiting, and diarrhea [63]), which tend to be dose-dependent and transient. Gijsman and colleagues recommended combining 5-HTP with a peripheral decarboxylase inhibitor (PDI) to block peripheral conversion of 5-HTP to serotonin, which decreases gut motility and hence GI upset [92]. Less common side effects include headaches, insomnia, and palpitations. 5-HTP in combination with SSRIs (fluoxetine) or MAOIs may cause serotonin syndrome [93]. However, in one study of single doses of 5-HTP (200 mg) administered to 26 patients taking fluoxetine, none developed signs or symptoms of serotonin syndrome [94]. Nonetheless, 5-HTP should be used with caution in patients taking antidepressants. There is little data regarding safety in pregnancy or in bipolar individuals, so caution is warranted in these populations.

Recommended doses based on the literature range from 20 to 3250 mg/day. The typical starting dose is 50 mg three times daily with meals, and the dose can be titrated upward

after 2 weeks as needed. Doses should be divided on a two to four times per day schedule, because of 5-HTP's relatively short half-life (4.3 ± 2.8 h) [63]. In summary, in view of its safety and previously supportive literature, 5-HTP appears to deserve reconsideration as an antidepressant, especially given the need for more rigorous clinical trials.

Inositol

Inositol, also called vitamin B8, is a sugar alcohol, a structural isomer of glucose that resides primarily in cell membranes. Myoinositol is the predominant of nine different isomers in humans. Inositol is found in beans, grains, nuts, and many fruits [95]. In the central nervous system, inositol participates in the synthesis of membrane phospholipids and is a precursor in the phosphatidylinositol (PI) cycle, producing inositol triphosphate (IP3) and diacylglycerol (DAG), vital second messengers that contribute to intracellular processes through neurotransmitter receptors [96].

An early finding of decreased inositol in the cerebrospinal fluid (CSF) of depressed patients led psychiatrists to consider treating depression with inositol [97]. Various lines of research comparing psychiatric patients with healthy controls have provided mixed evidence for psychotropic effects of inositol [63]. Levels of inositol in the frontal cortex of suicide victims and patients with bipolar disorder are lower than in healthy controls [98]. Myoinositol is likewise reduced in the frontal lobes of untreated depressed bipolar and unipolar patients [99]. On the other hand, acute (5–7 days) and chronic (3–4 weeks) lithium treatment of depressed bipolar patients was also associated with low frontal lobe myoinositol levels [95]. Magnetic resonance spectroscopy has yielded mixed results regarding changes of myoinositol levels in the cortex of medicated and unmedicated MDD patients [100]. Furthermore, baseline CSF inositol levels do not predict response to treatment [101, 102]. Because mood stabilizers are thought to work by stabilizing inositol signaling, mania could be secondary to excess inositol, and conversely, depression may be associated with an inositol deficit that could be reversed with supplementation [63].

There are approximately six published clinical trials (five placebo-controlled) of inositol for treatment of depression, most of which used inositol as augmentation of antidepressants and mood stabilizers in patients with unipolar and bipolar depression. Inositol outperformed placebo in three of five controlled studies, with two studies on unipolar depression producing negative results. Most of these comparisons did not achieve significance, however, probably due to small sample sizes. Other pilot studies have demonstrated efficacy in panic disorder, obsessive compulsive disorder (OCD), and bulimia nervosa [103]. This suggests a broad spectrum of action like that of SSRIs. On the other hand, studies in schizophrenia, attention deficit disorders, Alzheimer's, autism, and ECT-induced cognitive impairment have been negative [63]. Recommended doses range from 6 to 20 g/day, typically about 12 g/day divided on a two to four times a day basis. OCD may require higher doses [63].

Tolerability and safety appear good. Side effects may include modest increases in plasma glucose, gas, nausea, sleepiness, insomnia, dizziness, and headaches. There appear to be no toxic reactions or drug-drug interactions. Inositol-induced mania has been reported in bipolar patients, so in such cases, inositol should ideally be used in combination with a mood stabilizer. Inositol is not recommended for pregnant women, because of a risk of inducing premature uterine contractions [63].

Overall, the findings thus far suggest efficacy for inositol in alleviating mood disorders as well as anxiety disorders. Studies with larger sample sizes are sorely needed for more definitive conclusions, however.

Chromium

Chromium is a microelement involved in the metabolism of carbohydrates, proteins, and lipids. It is sold over the counter as a supplement for weight loss. Chromium deficiency may contribute to diabetes mellitus, and supplementation is thought to improve glucose tolerance in diabetics via stimulation of insulin action and insulin sensitivity. Chromium has also been proposed as an antidepressant with potential benefit in atypical depression, characterized by increased appetite, carbohydrate craving, and weight gain, all of which could be controlled by chromium [63].

While there is no clear relationship between chromium deficiency and depression, chromium has been shown to support monoaminergic neurotransmission and tryptophan transport across the BBB into the central nervous system (CNS). Chromium also stimulates serotonin (5-HT) synthesis and function and norepinephrine release. It decreases 5-HT 2A receptor activity in animals and humans and in rat studies has produced a significant increase in plasma and brain tryptophan and brain 5-HT. Chromium may also interact with glutamatergic pathways via the N-methyl-D-aspartate (NMDA) and the alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors. These mechanisms collectively support a potential antidepressant effect [63].

There are a few reports of note, with support for chromium in psychiatric populations. In a case series of five patients with dysthymia who were taking standard antidepressants, chromium supplementation led to remission [104]. In one RCT with 15 subjects with atypical depression, investigators found significant differences between chromium and placebo: response rates of 70% for chromium and 0% for

placebo and remission rates of 60% for chromium and 0% for placebo [105]. Another RCT with 113 subjects with atypical depression found no significant differences in depression severity improvement between chromium and placebo, but there was a notable effect on atypical symptoms, particularly carbohydrate cravings [106]. Other recent investigations have suggested benefit in premenstrual dysphoric disorder [107], and binge eating [108].

Chromium appears very safe and well tolerated, particularly in the picolinate form [63]. Reported side effects include early insomnia, tremor, and mild psychomotor activation, but no serious toxic effects. Vivid dreams have been reported; for which reason, chromium should best be taken in the morning. There is one report of uric acid renal stones, but it was not clear whether chromium was directly responsible [109].

Overall, the data supporting efficacy of chromium for atypical depression is encouraging, though preliminary. Increased appetite and carbohydrate craving seem to be particularly good targets. Recommended doses are in the range of 400–600 μg/day of the picolinate form. Further controlled trials should be carried out to characterize its efficacy as monotherapy and augmentation therapy, particularly in atypical depression.

Mitochondrial Modulators

There are several natural products thought to act by modulating mitochondrial activity, impacting on the electron transport chain. Nierenberg and colleagues have proposed that disruption in mitochondrial modulation could contribute to bipolar illness [110] and others have suggested a role in Alzheimer's disease [111]. Among these products are the previously mentioned N-acetylcysteine (see section on vitamin supplements), acetyl-L-carnitine (ALCAR), and alpha-lipoic acid (ALA).

Acetyl-L-Carnitine (ALCAR)

Carnitines are fatty acids that transport fatty acids into mitochondria and scavenge reactive oxygen species. They enter the mitochondria as acyl-carnitines and release energy when oxidized, forming acetyl coenzyme A, which then enters the citric acid cycle. Acetyl-L-carnitine (ALCAR) may carry out psychotropic effects by crossing the blood-brain barrier and protecting brain cells. It may reverse or slow down age-related degeneration in animals, including cognitive and motoric decline in rats. Other mechanisms include decreasing oxidative stress and reversing diminished reactivity to the environment [110].

Bersani and colleagues conducted a multicenter, double-blind controlled randomized 7-week study of ALCAR 1000 mg TID vs. fluoxetine 20 mg/day in 80 elderly patients with dysthymic disorder. ALCAR produced statistically significant improvement in depressive and anxiety symptoms per various clinician- and self-reported scales. Findings were similar for the fluoxetine group, but these individuals had a longer latency to response (2 weeks vs. 1 week). This suggests that ALCAR may carry out antidepressant effects through different mechanisms of action, possibly due to rapid support of neuronal activity [112]. An RCT comparing ALCAR 500 mg BID with amisulpride 50 mg daily in dysthymic patients found a clinically significant improvement in depressive severity in both treatment arms but no significant differences [113]. A study examining a combination of ALCAR 1000–3000 mg/day and alpha-lipoic acid (ALA) 600–1800 mg/day in bipolar depression found no significant advantage for the combination over placebo [114]. In a crossover study with 24 hospitalized elderly patients with depression, Tempesta et al. found a significant decrease in depression severity with ALCAR compared to placebo [115].

The body of research on ALCAR's potential antidepressant benefits has been reviewed by Wang et al., [116] who presented a cautiously optimistic perspective on studies published thus far, but emphasized the need for adequately powered, rigorously designed trials. Veronese et al. [117] performed a meta-analysis of 12 studies and found that ALCAR significantly decreased depressive symptoms compared to placebo or no intervention, with fewer side effects than antidepressants. The authors also called for large-scale, well-designed trials.

ALCAR has also been examined for other indications. A study examining ALCAR in children and adolescents with ADHD was negative [118]. A Cochrane review was not supportive of benefits in dementia [119]. However, a study found that ALCAR could reduce physical and mental fatigue and improves cognition in elderly patients [120]. A study of intravenous ALCAR in alcoholic patients found improvement of anhedonia, melancholic and negative symptoms, compared to oral ALCAR treatment [121].

Few cases of serious adverse effects have been reported. There is one case report of psychosis as an adverse effect [122] and one case report of mania recurrence in a patient using ALCAR for weight loss [123]. Overall, ALCAR appears mostly safe, and early evidence of efficacy appears to support further research.

N-Acetylcysteine (NAC)

N-acetylcysteine (NAC) has been shown independently to increase synthesis of glutathione (GSH), which in turn reduces oxidative stress. It prevents oxidative damage in the mitochondrial electron transport chain and protects brain cells. It may function similarly to lithium and valproate. Perhaps for this reason, most reported clinical trials of NAC in mood disorders have focused on bipolar disorder rather than unipolar depression. Because the clinical trials are relatively few, we will also include some studies in bipolar illness.

Berk and colleagues [124] performed a double-blind placebo-controlled trial in bipolar disorder with 75 subjects, randomized for 6 months to 2000 mg/day versus placebo added to treatment as usual. Results showed improvements in depressive severity and in global functioning in the NAC group compared with the placebo group. Berk et al. followed this with an 8-week open trial of NAC 2000 mg/day, followed by randomization to maintenance with NAC or PBO + TAU in 149 patients with bipolar disorder. Improvement in depression symptoms was observed during open phase but minimal change during maintenance [125]. Magalhães and colleagues [126] carried out a 6-month double-blind placebo-controlled trial in 15 bipolar subjects. NAC improved manic symptoms, while the PBO group had worsening of depressive symptoms.

A more recent study by Berk and colleagues in unipolar MDD found that remission and response rates were greater in the NAC group but required 16 weeks for separation from placebo [127]. Gastrointestinal and musculoskeletal side effects were more common in the NAC group. A systematic review and meta-analysis [128] examined five clinical trials of NAC in diverse patient samples, including two studies in bipolar depression, one in MDD, and two studies examining depressive symptoms in subjects with trichotillomania and heavy smoking, respectively. Overall, N-acetylcysteine produced lower depression scores on the Clinical Global Impressions-Severity of Illness scale and better global function compared to placebo, and tolerability of NAC was deemed good.

Overall, evidence for NAC is still very preliminary, particularly in unipolar depression, and more trials are needed.

Alpha-Lipoic Acid (ALA)

ALA is a cofactor for the pyruvate dehydrogenase complex. It functions to increase cellular uptake of glucose by boosting insulin sensitivity, and it also scavenges reactive oxygen species through antioxidant activity. Salazar suggests that given that insulin activity can increase tryptophan influx into the brain (and hence serotonin), increased insulin sensitivity through ALA supplementation could potentially treat depression [129]. Anecdotal evidence has been reported with some mood-related benefit in some people.

Studies in animals suggest possible antidepressant effects [130, 131], particularly in forms that involve BDNF deficiency [132]. A 2-week controlled study in diabetic patients compared intravenous ALA (600 mg/day) and Mexidol's (300 mg/day) effects on affective status, cognitive function, and quality of life, as well as on glycemic control. Both treatments reduced hyperglycemia and guilty feelings. ALA also reduced attention deficits [133]. A previously mentioned combination study of ALCAR and ALA in bipolar depression was not encouraging [114]. Reported adverse effects appear uncommon and may include allergic reactions, nausea, and hypoglycemia.

While ALA appears well tolerated and safe, more clinical trials in mood disorders are needed to determine whether ALA deserves a place in the psychopharmacological armamentarium.

Coffee and Caffeinated Drinks

While coffee and other caffeinated drinks are immensely popular worldwide and known for their stimulating effects, there is relatively little investigation as to whether coffee possesses antidepressant potential, either as a preventative or therapeutic agent. There is, nonetheless, some compelling early evidence.

In a large observational study of 50,739 women, the Harvard School of Public Health reported that the risk of depression had an inverse association with caffeinated coffee consumption. Consumption of four or more cups of caffeinated coffee per day reduced risk of depression by 20% compared to women who drank little or none, suggesting that caffeine may have a protective effect against depression [134]. Similarly, a 2013 investigation in a Japanese sample suggested that consuming four cups of green tea or two cups of coffee daily might offer protection against depression [135].

In an analysis of 11 observational articles totaling 330,677 participants in seven studies, the risk of depression decreased by 8% for each additional cup of coffee consumed each day, suggesting a dose-response relationship. The risk of depression decreased faster and the association achieved significance at caffeine consumption levels between 68 and 509 mg/day (the equivalent of one to five regular cups). The authors concluded that the use of coffee and caffeine was significantly associated with a decreased risk of depression [136]. Another study of Finnish men who drank roughly eight daily cups of coffee reported a 77% risk reduction for depression [137]. Not surprisingly, many individuals with depression may turn to coffee as a means of self-medication [138].

If coffee can help prevent depression, how might it work? Given the known link between depression and increased inflammatory activity [139], and the fact that coffee has anti-inflammatory effects [140], it is possible that regulated coffee use could benefit individuals with mild depressive symptoms. An additional mechanism of action for coffee is the enhancement of serotonin production [141], which may in turn stimulate synthesis of neurotransmitters relevant to mood regulation. Other lines of investigation have shown that certain decaffeinated coffees, specifically containing high polyphenol levels and chlorogenic acids, in particular 3-caffeoylquinic acid (3-CQA), the main polyphenol in coffee, also improve mood and performance [142]. The postulated anti-inflammatory and serotonergic effects of coffee suggest that, if used properly, it could have beneficial effects in depressed individuals.

It should be noted, however, that the increased popularity of caffeinated energy drinks, particularly among adolescents

and young adults who consume "energy drinks," has resulted in some serious adverse events in cases of excessive consumption. These include tachycardia, vomiting, cardiac arrhythmias, seizures, and even death, as well as longer-term problems such as obesity and dental enamel erosion [143]. In view of the above, clinicians should routinely inquire about caffeine use in their patients with depression.

Given the ubiquity of caffeinated drinks, their popularity, affordability, and easy accessibility, if certain types of coffee are indeed capable of preventing or treating depression, they could easily find a niche in the psychopharmacologist's armamentarium for depression. Prospective studies examining efficacy in acute mood disorders may prove valuable.

Clinical Application and Recommendation for Practitioners

Natural remedies represent a promising treatment approach for depression because of increasing evidence of efficacy and safety. With time, they will likely become more closely integrated into medical and psychiatric practice. As of this writing, however, much more work needs to be done to better understand these treatments and characterize their proper place in the psychiatric armamentarium. For now, clinicians should proceed with caution. The best candidates for natural remedies are patients with mild illness who have a strong interest in trying something natural. These individuals may have little to lose by trying one of these natural remedies, and in the worst-case scenario, they can always switch to a more proven therapy. At the other extreme are patients who have tried many registered medications without success, either due to limited efficacy or bothersome side effects. These individuals may also benefit from the use of natural remedies, either in combination with or as an alternative to standard agents. However, these patients have more treatment-resistant illness and may therefore not be the optimal candidates. As with any treatment, the clinician should have a thorough discussion with the patient about the pros and cons of natural remedies, so that the patient can make an informed decision about how to proceed. Table 15.1 provides a summary of the key facts about the remedies reviewed in this chapter, including recommended doses, reported side effects, and interactions with other drugs.

Table 15.1 Natural remedies for depression: doses and adverse effects/interactions (in alphabetical order)

Remedy	Suggested doses	Adverse effects/interactions
Acetyl-L-carnitine (ALCAR)	1000–3000 mg/day	Psychosis, mania (rare)
Alpha-lipoic acid (ALA)	600–1800 mg/day	Allergic reactions, nausea, hypoglycemia
Chromium	400–600 μg/day (picolinate form)	Early insomnia, tremor, mild psychomotor activation, vivid dreams, possible uric acid renal stones
Coffee	68–509 mg/day (equivalent of 1–5 regular cups)	Insomnia, tachycardia, vomiting, cardiac arrhythmias, seizures, obesity and dental enamel erosion, death (particularly with high-caffeine energy drinks)
Folic acid	5-Methyltetrahydrofolate (5-MTHF; Deplin): 7.5–15 mg/day	Allergic reactions
	Folic acid: 200–500 μg/day	
	Folinic acid (leucovorin): 15–30 mg/day	
5-Hydroxytryptophan (5-HTP)	20–3250 mg/day	Nausea, vomiting, diarrhea, headaches, insomnia, palpitations; possible serotonin syndrome in combination with standard antidepressants
Inositol	6–20 g/day (possibly higher doses in OCD)	Modest increases in plasma glucose, gas, nausea, sleepiness, insomnia, dizziness, headaches; mania in bipolar patients; premature uterine contractions
N-acetylcysteine (NAC)	2000 mg/day	Gastrointestinal and musculoskeletal discomfort
Omega-3 (n-3) fatty acids (EPA and DHA)	1000–2000 mg/day (some studies administer up to 10 grams/day for bipolar illness)	Gastrointestinal symptoms; cycling to mania in bipolar patients
Rhodiola rosea	100–680 mg/day	Allergy, irritability, insomnia/vivid dreams, fatigue, and unpleasant sensations, especially at high doses; mild serotonin syndrome with paroxetine
S-adenosyl-L-methionine (SAMe)	200–3200 mg/day (some may require higher doses)	GI upset, insomnia, anorexia, dry mouth, sweating, dizziness, and nervousness; mania in bipolar patients
St. John's wort (*Hypericum perforatum* L.)	300–1800 mg/day divided BID-TID	Dry mouth, dizziness, constipation, photosensitivity, serotonin syndrome when combined with SSRIs; mania in bipolar patients; adverse interactions with warfarin, cyclosporin, oral contraceptives, theophylline, fenprocoumon, digoxin, indinavir, zolpidem, irinotecan, and olanzapine
Vitamin supplements	Varied	Possible concerns about hypervitaminosis in some cases

FAQs: Common Questions and Answers

Q1. Are natural remedies safe?

A1. For the most part, natural remedies are safe and often have less frequent and milder side effects compared to registered medications. However, many can have potentially dangerous side effects and interactions with other drugs. Consequently, they should be used with the same caution as registered medications, and preferably under supervision of a medical professional.

Q2. Are natural remedies better than registered medications?

A2. There are relatively few studies comparing natural remedies against registered medications. Some comparisons suggest that natural remedies may work as well as their FDA-approved counterparts, but many of these studies are not as rigorous as they need to be to make firm conclusions.

Q3. Can natural remedies be combined with regular medications?

A3. Many natural remedies can be combined with standard medications. Often the effects may be synergistic and produce a better effect than either treatment alone. However, care needs to be taken with certain natural products such as St John's wort, because of risk of interactions.

Q4. How fast do natural antidepressants work?

A4. Most natural psychotropics tend to work in about the same time frame as registered medications. For antidepressants, typically 6–12 weeks of treatment may be needed before determining whether the remedy is effective or not.

Q5. Should I recommend natural remedies to my patients? Which patients are the best candidates?

A5. It is generally safer for clinicians to stick with FDA-approved drugs, since those have more evidence for efficacy and safety. However, if a patient is interested in trying a natural remedy, the best candidates are patients with milder forms of illness. Sometimes patients with resistant illness who have tried many therapies unsuccessfully, either due to lack of efficacy or side effects, may also consider trying alternative treatments.

Q6. What if my patients are taking natural remedies without telling me?

A6. If you suspect that a patient may be taking a remedy without your knowledge (a common occurrence), you should ask them about it in a nonjudgmental manner and mention that many of these treatments are effective and perfectly appropriate to use but that as their treater, you need to know about it so that you can make sure not to prescribe something that could have an adverse interaction with the remedy they are taking.

Q7. Are natural remedies addictive?

A7. There is no evidence that any of the natural remedies discussed here are addictive or result in dependence, except perhaps coffee, which often can result in caffeine dependence and withdrawal upon sudden discontinuation. Other natural products such as sedatives and stimulants not covered here may be subject to abuse in some cases and should therefore be managed carefully.

Q8. Now that marijuana is being increasingly legalized, will doctors be prescribing it regularly?

A8. Not necessarily. There is still a great deal of reluctance in the medical profession, and rightly so, because there is limited systematic data about the risk/benefit ratio of the use of marijuana in psychiatric disorders.

Q9. How can I learn more about natural remedies? Is the Internet a good source of information?

A9. The Internet certainly has many sources of information about natural remedies. Some are more reliable than others, however, and biases do exist. Often websites such as PubMed or clinicaltrials.gov are good sources, since they reflect what the clinical trials are showing about these therapies. You can also take continuing education courses or attend academic conferences that focus on these remedies.

Q10. Should patients go ahead and self-medicate with natural over-the-counter products?

A10. In general, it is not a good idea for patients to self-medicate for serious conditions such as depression. These treatments are best used under clinician supervision.

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