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Review

Second-tier natural antidepressants: Review and critique

Nadia Iovieno [a,b,*], Elizabeth D. Dalton [a], Maurizio Fava [a], David Mischoulon [a]

[a] Depression Clinical and Research Program at Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[b] Department of Psychiatry, University of Pisa, Pisa, Italy

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ABSTRACT

The use of Complementary and Alternative Medicine (CAM) for physical and mental problems has increased significantly in the US over the past two decades, and depression is one of the leading indications for the use of CAM. This article reviews some of the lesser-known natural products with potential psychiatric applications that are starting to emerge with some scientific and clinical evidence and may constitute a next wave of natural antidepressants: *Rhodiola rosea*, chromium, 5-Hydroxytryptophan (5-HTP) and inositol. Background information, efficacy data, proposed mechanisms of action, recommended doses, side effects, and precautions are reviewed. We found some encouraging data for the use of these natural products in specific populations of depressed patients. *R. rosea* is an adaptogen plant that can be especially helpful in treating asthenic or lethargic depression, and may be combined with conventional antidepressants to alleviate some of their common side effects. Chromium has a beneficial effect on eating-related atypical symptoms of depression, and may be a valuable agent in treating atypical depression and seasonal affective disorder. Inositol may be useful in the treatment of bipolar depression when combined with mood stabilizers. Evidence for the clinical efficacy of 5-HTP is also promising but still preliminary. Although more well-designed and larger controlled studies are needed before any substantive conclusions can be drawn, the available evidence is compelling and these natural products deserve further investigation as a possibly significant addition to the antidepressant armamentarium.

Contents

* Corresponding author. Depression Clinical and Research Program, Massachusetts General Hospital, 50 Staniford Street, Boston, MA 02114, USA. Tel.: +1 857 294 5048; fax: +1 617 726 7541.
E-mail address: niovieno@partners.org (N. Iovieno).

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1. Introduction

In the last decade there has been a significant increase in the use of Complementary and Alternative Medicine (CAM) for physical and mental health problems in the US and worldwide. The 2007 National Health Interview Survey (NHIS) reported that 38% of US adults and approximately 12% of children had used some form of CAM in the past 12 months, especially natural products. Depression, anxiety, and insomnia are among the most common reasons for people to use complementary therapies (Kessler et al., 2001), and persons with major depressive disorder (MDD) may be more likely to use CAM therapies than those without it (Unützer et al., 2000). Many patients self-treat their mood disorder with CAM without professional supervision, and often without disclosing it to their psychiatrist or primary physician (Elkins et al., 2005). Moreover, most patients who use CAM remedies also take prescription antidepressants concurrently, risking potentially dangerous adverse herb/drug interactions. While most natural psychotropics are generally considered safe, they are not necessarily risk free, and the common public misconception that natural equals safe has been belied by various reports of toxic reactions from these agents, which may be due to intrinsic toxicity, contamination, or interaction with other drugs.

Although a multitude of natural medications are available for the treatment of mood disorders, the evidence for their effectiveness remains limited for most, if not demonstrated at all for many. According to Astin et al. (1998), the five most widely used CAM approaches are acupuncture, chiropractic, homeopathy, herbal medicine, and massage. A few natural psychotropics have been more extensively examined in reasonably well-designed, placebo-controlled, double-blind studies, and in systematic reviews and meta-analyses. Well-studied products include St John's Wort, S-adenosyl-L-methionine (SAMe) and Omega-3 fatty acids (Mischoulon, 2009), for which there is a growing consensus of antidepressant effectiveness and safety. Other alternative therapies that are also gaining acceptability as potential antidepressants include folate (Fava and Mischoulon, 2009), acupuncture (Smith et al., 2010) and exercise (Freeman, 2009; Greer and Trivedi, 2009).

There are also other products that are emerging with early scientific and clinical evidence for effects on mood and may deserve evaluation as a next wave of potential natural antidepressants, both as monotherapy and as adjuncts to well established treatments. This article will review four of these second-tier natural products for mood disorders: *Rhodiola rosea*, Chromium, 5-Hydroxytryptophan and Inositol.

2. Methods

A Pubmed/Medline literature search was performed, using the search terms *Complementary Medicine*, *Complementary Therapy*, *Alternative Medicine*, *Alternative Therapy*, *Depression*, *Depressive Disorder*, *R. rosea*, *Chromium*, *5-Hydroxytryptophan* and *Inositol*. We included systematic reviews, meta-analyses, RCTs, case control studies, open studies, case series, and case studies for each therapy. We obtained the original articles where possible, and also hand-searched for cross-referenced articles and books. Searches were restricted to English language publications. Restrictions on year of publication were not applied.

3. *R. rosea*

R. rosea is a popular plant widely distributed at high altitudes in the mountainous regions of Europe and Asia, where it is also known as “golden root” or “arctic root”. The roots of the plant have been used for centuries in the traditional medicine of Asia, Scandinavia, and Eastern Europe as a health-enhancing supplement for stimulating the nervous system, enhancing physical and mental performance, alleviating fatigue, psychological stress, depression, impotence, and preventing high altitude sickness. *R. rosea* has been classified by Russian researchers as an adaptogen, a substance that nonspecifically increases the resistance of an organism to a variety of chemical, biological, and physical stressors.

3.1. Mechanisms of action

R. rosea contains many biologically active substances including flavonoids, monoterpenes, triterpenes, phenolic acids, phenylethanol derivatives (salidroside and p-tyrosol) and phenylpropanoid glycosides such as rosin, rosavin, and rosarin, comprehensively referred to as rosavins and specific to this plant. The stimulating and adaptogenic properties of *R. rosea* are attributed specifically to p-tyrosol, salidroside, rosavins, and additional phenolic compounds, while the high content in organic acids and flavonoids contributes to the strong antioxidant properties of the plant (Ming et al., 2005). According to the revised 1989 Soviet Pharmacopeia, *R. rosea* extracts are standardized for both rosavins and salindroside. The extracts used in most human clinical studies are standardized to minimum 3% rosavins and 0.8% salidroside, because the naturally occurring ratio of these compounds in *R. rosea* root is approximately 3:1.