SAINT JOHN'S WORT AS A TREATMENT OPTION FOR
MILD TO MODERATELY SEVERE ADOLESCENT DEPRESSION

By

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Abstract

This paper discusses the herbal supplement Saint John’s Wort, *Hypericum perforatum*, and its potential to treat mild to moderately severe depression in adolescents. Depression is a serious illness that affects millions of adolescents across the globe. Depression is characterized by symptoms of unhappiness, anhedonia, and low self-esteem. If left untreated it can lead to substance abuse disorders and even suicide. This paper discusses what is known of depression, focusing on an overview of the monoamine hypothesis of depression. Under the monoamine hypothesis, treatment for depressed adolescents often includes antidepressants. These antidepressants are primarily of the monoamine reuptake inhibitor class, which have been shown to carry caustic side effects when prescribed to adolescents, and even carry a black box label warning of an increased risk of suicide in adolescents. Hyperforin, the primary biologically active component of *Hypericum*, has been shown to inhibit monoamine reuptake in a manner similar to that of antidepressants, and is similarly effective. Additionally, *Hypericum* extracts are less expensive and significantly better tolerated. If taken under the supervision of a physician, *Hypericum* extract could provide an effective alternative treatment for adolescents suffering from moderately severe depression, without the side effects and risks associated with synthetic antidepressants.
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Introduction

Major Depressive Disorder is a crippling mental illness that makes a struggle out of day-to-day life. It is characterized by symptoms of lack of joy, lack of motivation, and low self-esteem. Depression ranks among the most common mental illnesses in the world. A survey undertaken by the U.S Department of Health and Human Services in 2012 estimated that 6.9 percent of American adults age 18 or over had had at least one major depressive episode in the past year (Substance Abuse and Mental Health Services Administration 2013). This prevalence is particularly disturbing because depression can manifest as severely debilitating or even deadly in the depressed patient. Major depressive disorder accounts for 3.7 percent of all U.S. years lost to premature mortality and disability, and 8.3 percent of all U.S. years lived with disabilities (Murray 2013). It is estimated that by the year 2020, depression will have risen to become one of the leading causes of disability, second only to heart disease (Peveler 2002). About 60 percent of suicides are associated with mood disorders like depression (Mann 2005).

These statistics document depression as observed in the adult population. However, depression is not limited to adults. The National Comorbidity Survey Adolescent Supplement, undertaken in the year 2012, shows that about 11 percent of adolescents have of have had a depressive disorder by the time they reach 18 years old. (Kessler 2012). This is particularly disturbing, as studies show that depression in adolescence is linked to substance abuse later in life, as well as an increased risk of suicide (Levy 1989).

Though depression is becoming increasingly prevalent in our society, most depression is manageable. Much is understood about the pathology of depression, and great strides have been made as to the treatment of both the symptoms of depression and the underlying physiological
pathologies of the illness. Medications prescribed for the treatment of depression are varied in their mechanisms of action, and the wide range of antidepressants available for treatment provide practitioners with many options that can be tailored to suit an individual patient’s depressive symptoms. Antidepressant medications are more effective than placebo, and have been shown to give as much as a 50 percent reduction in depression scores in both major and mild depressions in adults (National Collaborating Centre for Mental Health 2009). When combined with cognitive behavioral therapy, antidepressants increase in efficacy. Through aggressive treatment and combination drug-behavioral therapy, most adult depression is manageable.

The treatment of depression in adolescents is significantly more difficult. The pathology of major depressive disorder in adolescents is not as well-understood as is the pathology of adult depression. Current thought sees adolescent depression and adult depression similarly, and an adolescent’s treatment options are adapted from pathologies and behaviors present in depressed adults. Treatment options for adolescent depression are derived from what works in treating adult depression. Cognitive behavioral therapy represents the most promising method of treatment of adolescent depression, but antidepressant are commonly prescribed in mild to moderately severe depressions which persist through behavioral therapy. However, the number of antidepressants currently approved for use in adolescents in the United States is few. Of the most cutting-edge antidepressant medications, the selective serotonin reuptake inhibitors, only Fluoxetine has been approved for use in adolescents. And, though a comprehensive study found that adolescent response rates for Fluoxetine were a promising 81 percent after 18 weeks of treatment (TADS 2004), the use of antidepressants for the treatment of depression in adolescents brings to the table new risks.
The most important risk associated with treating adolescent depression with antidepressants is an increased risk of suicide. In 2004, the FDA launched a comprehensive review of all available clinical trials assessing antidepressant use in children and adolescents. Out of a patient base of 2200 children, roughly 4 percent experienced suicidal thoughts or behavior. Though no suicides were completed, the rate of suicidality was double that of adolescents treated with placebos (National Institute of Mental Health, 2006). The FDA has issued a “black box” warning for most antidepressants, warning that “antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults when the medicine is first started” (Food and Drug Administration 2007). This warning was based on early findings, and, though many subsequent studies have found countries with high rates of SSRI prescription have lower rates of adolescent suicide (Olfson 2003, Gibbons 2006), the black box warning subsists to this day. In addition to a disputed increased risk of suicide, common antidepressants often carry with them side effects that can be particularly distressing for adolescents. Though it is generally tolerated well, Fluoxetine alone carries such risks as problems sleeping, headaches, upset stomach, and changes in weight or appetite. Other antidepressant variations, such as the tricyclic class or the monoamine oxidase inhibitors, carry such strong risks as dangerously high blood pressure, and patients taking these antidepressants must adhere to strict dietary limits. As such, they are usually avoided entirely when treating depression in adolescents. Thus, pharmacological options are limited. Side effects and black box warning considered, current antidepressants leave a lot to be desired in the treatment of adolescent depression.

There is potential in standardized preparations of Hypericum perforatum, Saint John’s Wort, for a pharmacological approach to adolescent depression which carries fewer side effects and fewer stigmas than do traditional synthetic antidepressants. Saint John’s Wort has been used
as a supplement in the treatment of depression for thousands of years, and has only recently come under scrutiny by the scientific community. Studies show that the colloquial use of Hypericum is not unfounded. A comprehensive review undertaken by the Cochrane Collaboration confirmed that extracts of Hypericum perforatum are more effective than placebo in reducing depression scores. Additionally, Hypericum extract is nearly as effective as SSRIs in treating mild to moderately severe depression (Linde 2008). Saint John’s Wort is made more attractive by the fact that it carries with it very few side effects. The greatest concern for a patient taking Hypericum extract is that the biologically active ingredients in the plant can lead to dangerous drug interactions if not taken under the supervision of a physician. However, reviews have shown it to be better tolerated than synthetic antidepressants (Linde). As of yet, few studies have been done assessing the efficacy of Saint John’s Wort in treating adolescent depression.

These facts considered, Hypericum extract seems a desirable candidate to fill a niche role in the treatment of mild to moderately severe adolescent depression. The supplement, were it to be regulated by the FDA in America, could provide practitioners with a first-line treatment option for patients wary of the risks associated with current synthetic antidepressants.
Depression

In order to show that *Hypericum* extract offers a promising option in the treatment of adolescent depression, basic background as to the physiopathology of depression must be discussed.

Depression is a mental disorder that is commonly characterized by persistent low mood. It affects a wide range of ages, including children, adolescents, and adults. Symptoms of depression manifest in similar ways in both adolescents and adults. Generally, low mood manifests itself in a number of ways, and patients suffering from depression will often exhibit symptoms of anhedonia and low self-esteem. Additional symptoms may include lethargy, irritability, a reduced sex drive, insomnia, hypersomnia, and, rarely, psychosis. In adolescents, the most common symptoms of depression include anhedonia, low self-esteem, and irritability (National Institute of Mental Health 2008). These symptoms combine in a patient to produce a mental state which can adversely affect all aspects of the patient’s life.

Depression diagnosis is based on a mental status examination. While primarily performed by a psychiatrist, non-psychiatrist medical professionals, such as primary care physicians, may also be trained to perform a mental status examination (Sharp 2002). Such an examination typically occurs when a patient presenting symptoms of depression seeks medical help for those symptoms. There is no laboratory test to confirm major depressive disorder, so ruling out other possible causes for a patient’s depressive symptoms must occur. Because depression shares symptoms with many unrelated diseases and dysfunctions, a series of physiological tests are ordered for a patient presenting symptoms of depression. These tests include blood tests for hypothyroidism, as well as an assay of electrolytes and serum calcium to
test for underlying metabolic disturbance. Erythrocyte sedimentation rate is also tested, to rule out systemic infection (Dale 2008). Such tests are standard for both adults and adolescents presenting depressive symptoms. In the absence of evidence of alternative diagnoses, a diagnosis of depression may be made by a trained primary care physician. The depressed patient may be referred to a psychiatrist for more thorough mental status examinations. The latter is commonly the case for adolescents presenting depressive symptoms (Sharp).

The ultimate diagnosis for depression in the United States is based off of the American Psychiatric Association’s *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR). (American Psychiatric Association 2000). The DSM-IV-TR classifies depression as a mood disorder characterized by single or recurrent major depressive episodes. Major depressive episodes are diagnosed by the symptoms of anhedonia and depressed mood, and a diagnosis may be conferred if one of the two is present in the patient, whether that patient be an adult or an adolescent. Major depressive episodes can be assessed individually to determine the severity of the patient’s major depressive disorder. Depressive episodes are categorized as mild, moderate, or severe, based on how adversely they affect the patient’s life. If a patient experiences a major depressive episode, and all other possible causes of depressive symptoms are ruled out, the patient may be diagnosed with clinical depression.

**Monoamine Hypothesis**

The underlying causes for depression are numerous, and the lack of biological markers for depression means that it is difficult to pin down any one source as the cause of single or recurrent major depressive episodes in adults or adolescents. Depression has been linked to a
very wide array of both psychological and biological causes, but the monoamine hypothesis is thus far the most studied and widely accepted biological explanation for depression. Most pharmacological drugs for depression address chemical imbalances explained by the monoamine hypothesis; this includes *Hypericum* extract. The monoamine hypothesis does not account for all phenomena observed in a depressed individual, and further research into biological models of depression has shown that the monoamine hypothesis is a simplified component of a more encompassing biological model for depression. However, current treatment options address the monoamine hypothesis. The monoamine hypothesis of depression claims that improper regulation of certain monoamine neurotransmitters in the brain is the cause of depressive symptoms (Nutt 2008). The monoamines most commonly studied under this hypothesis include serotonin, dopamine, and norepinephrine.

Studies have long linked an irregular balance of monoamine neurotransmitters to the symptoms commonly associated with depression. A deficiency in the monoamine serotonin (5-hydroxytryptamine, or 5-HT) has been related to anxiety and compulsion (Nutt 2008), and has been shown to correlate with the depressive symptom of fatigue (Marin 2005). Decreased transmission of norepinephrine (NE) has been associated with low energy, problems of concentration and cognition, and decreased alertness (Moret 2011). Dopamine (DA) deficiencies have been associated with an inability to experience pleasure, as well as a decrease in motivation (Dunlop 2007). The metabolic pathways of all three of these neurotransmitters have been shown to cross at multiple places in the brain, and 5-HT has been shown to regulate pathways that regulate the production and uptake of both NE and DA (Mandell 1979). In light of this observation, it has been suggested that a deficiency of all three monoamine neurotransmitters produces the unique catalogue of symptoms each depressed patient expresses. Thus, a patient
who experiences a major 5-HT deficiency will experience different depressive symptoms than will an individual who experiences a major norepinephrine deficiency. Although this hypothesis was developed to explain major depressive disorder in adults, the monoamine hypothesis has been supported in adolescents. Studies have shown that an increase in brain serotonin levels can lead to decrease in the severity of depressive symptoms in adolescents with major depressive disorder (TADS).

One implication of the monoamine hypothesis of depression is that certain metabolic activities that cause irregularities in 5-HT, NE, and DA can be linked intimately to depressive episodes. Such links between metabolic activity and abnormal monoamine brain concentration are numerous, and no single metabolic interaction is responsible for the onset or recurrence of depressive episodes (Boer 2006). However, certain key regulators of monoamine metabolic pathways of breakdown and uptake have been extensively studied in patients with major depressive disorder.

Among these monoamine regulators is the monoamine oxidase (MAO) enzyme family. MAO is an enzyme family located in the mitochondrial outer membrane of cells, and is found in both neurons and astroglia in the brain. The primary action of MOA is to catalyze an oxidative deamination reaction of monoamines into aldehydes and ammonia (Edmonson 2004). This oxidative deamination is performed by two different MAOs: MAO-A and MAO-B. MAO-A primarily breaks down serotonin, epinephrine, norepinephrine, and melatonin (see Figure 1, point A). MAO-B primarily breaks down phenethylamine and benzylamine. Dopamine, tryimine, and tryptamine are broken down by both MAO-A and MAO-B (Tipton 2004). Because MAO enzymes catalyze the breakdown of monoamine neurotransmitters, they have long been correlated with the reduced concentration of 5-HT, NE, and DA observed in depressed patients,
adult and adolescent alike. Overactivity of MAO enzymes is at least partially responsible for the decreased concentration of monoamines observed in an individual with major depressive disorder (Meyer 2006).

![Image](https://www.cnsforum.com/educationalresources/imagebank/antidepressants/drug_moai_2)

Figure 1

The action of MAO-A in the breakdown of 5-HT and NE.

Image adapted from:

https://www.cnsforum.com/educationalresources/imagebank/antidepressants/drug_moai_2

Though the actions of MAOs in monoamine imbalance have been established in a few cases, in recent years studies have shown that the action of monoamine transporters (MATs) may contribute more heavily to the abnormal concentration of monoamines observed in depressed
patients. MAT’s are integral plasma membrane proteins that regulate the concentration of monoamine neurotransmitters in the neuronal synaptic cleft (Torres 2003). The three classes of MAT are the serotonin transporter (SERT), norepinephrine transporter (NET), and the dopamine transporter (DAT). All are Na+/Cl− dependent, substrate-specific transporters that regulate the reuptake of released monoamines into the presynaptic terminal from their position in the synaptic cleft of the neuronal synapse (see Figure 2) (Ramamoorthy 2010). Irregularities in the actions of SERT and NET, specifically, have been observed in depressed individuals. Overactivity of these two MATs has been linked with decreased 5-HT and NE availability in the synaptic cleft in the depressed individual, and it has been suggested that observed polymorphic variations in MAT genes could be correlated with major depressive disorder (Torres), though more research is needed to rule out other causes for the MAT dysfunction observed in depressed patients.

Figure 2

Monoamine neurotransmitter release and reuptake at the synapse.

Though the monoamine hypothesis of depression goes a long way in explaining the pathophysiology of the disease, it is not an all-encompassing hypothesis. Recent shifts in the attitudes of researchers and practitioners has shown that, while it was once heralded as the answer to major depressive disorder, the monoamine hypothesis is really only a smaller piece of a pathophysiology that is not completely understood (Boer 2006). Likewise, the two mechanisms of action discussed here (the actions of MAOs and MATs) are two of the most researched causes of monoamine depletion, but they are not the only causes that support the monoamine hypothesis of depression. What has been stated above is merely a brief overview of two widely researched and generally accepted mechanisms which contribute to the greater pathophysiology observed. Over the last 30 years researchers have found much evidence which supports the hypothesis, but also much evidence that pokes holes in the monoamine hypothesis of depression (Hirschfeld 2000). These two mechanisms of depression are discussed because they have been observed in both adults and adolescents, and they have been observed to be affected by *Hypericum* extract.

**Treatment of Depression under the Monoamine Hypothesis**

Treatment for overactive metabolism and reuptake of monoamines has been the primary pharmacological approach to depression for over 50 years. Most drugs currently approved for the treatment of depression address the monoamine hypothesis, in that they either reduce the activity of monoamine oxidase enzymes or they reduce the efficacy of monoamine transporters. Both monoamine oxidase inhibitors and monoamine reuptake inhibitors have the goal of increasing the total amount of monoamine available in the synaptic cleft.
Drugs which decrease the activity of MAO enzymes are known as monoamine oxidase inhibitors (MAOIs). MAOIs approved and currently on the market work through the inhibition of the MAO enzyme, either through nonselective inhibition of MAO-A and MAO-B, or selective inhibition of either. By inhibiting a crucial step in monoamine metabolism, MAOIs increase the concentration of monoamines available to the body. Though they are effective, MAOIs are considered by some to be dangerous because they interact adversely with a wide variety of compounds found in common diets and medicines, particularly the tyrosine breakdown product tyramine (Fiedorowicz 2004). Because of this, MAOIs have seen historical use as a final option pharmaceutical treatment for those suffering with depression, and are often overlooked in the treatment of adolescents with depression. MAOIs have been shown to be effective especially in the treatment of atypical and bipolar depressions (Fiedorowicz). A study of MAOI efficacy showed that MAOIs were effective at treating depression in as many as 56% of clinical trials, out of 59 total trials surveyed (Amsterdam 2005).

Drugs which reduce the efficacy of monoamine transporters are known as monoamine reuptake inhibitors (MRIs). Many classes of MRI drugs are currently on the market for the treatment of depression, but most MRIs prescribed are selective serotonin reuptake inhibitors (SSRIs). These work specifically to block SERT active transport of serotonin into the presynaptic terminal, increasing levels of 5-HT available to the neuronal postsynaptic receptor (Preskorn 2004). Though SSRIs remain the most prescribed MRI, the second generation of MRIs feature reduced selectivity of the reuptake inhibition mechanism. As such, many drugs on the market work to inhibit reuptake of both 5-HT and NE (Boot 2005). MRIs are commonly prescribed as a first-line pharmaceutical treatment for patients suffering from severe depression (Preskorn), and are often paired with cognitive therapy in patients with mild to moderately
severe persisting depression. MRIs are often prescribed to children and adolescents presenting mild to moderately severe cases of depression, but there is dispute as to the efficacy of this subset of medication, particularly in children (Hetrick 2012).

When treating mild to moderately severe depression in adolescents, pharmaceutical approaches hinging on the monoamine hypothesis have been the traditional approach. The primary mode of pharmacological treatment for adolescent depression is MRIs, with SSRIs such as Fluoxetine commonplace. However, results have been mixed. A comprehensive study undertaken by the Treatment of Adolescent Depression Study Team showed that adolescents with depression who are exposed to pharmacological treatment with SSRIs show significant reduction in depressive symptoms (TADS). After 36 weeks of Fluoxetine SSRI treatment, adolescents showed an 81 percent response rate. Though poorly understood, medications addressing monoamine deficiencies appear to give positive results in some studies. However, it is not always clear that MRIs are significantly superior to placebo in clinical trials assessing SSRI antidepressants in adolescents (Hetrick). Only more research can determine the intricacies of the pathophysiology of adolescent depression, and time will tell whether or not approaches under the monoamine hypothesis are effective in the way that they are thought to be.
**Saint John’s Wort**

The subject supplement of this paper is extract of *Hypericum perforatum*, colloquially known as Saint John’s Wort. *Hypericum* is a perennial flowering herb found across the globe (see Figure 3). It has a 2000 year history of use as a pain-killer and an anti-inflammatory agent, among other uses, and was prescribed as early as the time of Hippocrates (Klemow 2011).

![Hypericum perforatum](http://commons.wikimedia.org/wiki/File:Hypericum_perforatum-IMG_4353.jpg)

*Figure 3*

*Hypericum perforatum*, Saint John’s Wort.

Image from: http://commons.wikimedia.org/wiki/File:Hypericum_perforatum-IMG_4353.jpg

Research has found that the basis for use of Saint John’s Wort in traditional medicine is not groundless; the herb has been discovered to contain seven different medicinally active compounds, and approximately 20% of compounds extractable from Saint John’s Wort are biologically active (Nahrsedt 1997). These compounds range in their effects on the body, from antibacterial (Bystrov 1975) to anticancer (Schempp 2002). However, perhaps no aspect of
*Hypericum perforatum* has been studied as much as its ability to treat mild to moderate depression in adults.

*Hypericum* extract affects the body in ways understandable through the lens of the monoamine hypothesis. Saint John’s Wort acts on the body through mechanisms similar to today’s synthetic antidepressants: it acts both to inhibit the enzyme monoamine oxidase and to inhibit the reuptake of monoamines at the synaptic cleft. Though the exact mechanisms of both actions have yet to be deciphered in full, the effects can be observed. Just as in the case of synthetic antidepressants, extracts of *Hypericum* increase the total concentration of monoamines available to the postsynaptic neuron.

**Saint John’s Wort Inhibition of Monoamine Oxidase**

Initial research into the antidepressant effects of *Hypericum* extract led researchers to believe that Saint John’s Wort’s antidepressant qualities came from its ability to act as an MAO inhibiter. *Hypericum* extract was initially shown to have action similar to that of the MAOI class of antidepressant drugs, thought to be due to the actions of the naphthodianthrone hypericin. Hypericin represents the most prevalent naphthodianthrone in standardized extracts of *Hypericum Perforatum*, and is commonly seen on the market standardized at concentrations between .1% and .3% (Robbers 1999). In early *in vitro* experiments, Hypericin was shown to irreversibly inhibit the action of both MAO-A and MAO-B, with a high affinity for MAO-A (Suzuki 1984). However, further studies have shown that hypericin’s ability to inhibit the action of monoamine oxidase is not as great as initially demonstrated. It has been determined that it is not hypericin which is responsible for MOA inhibition in *Hypericum* extract, but rather the
flavonoid compounds quercetin, luteolin, and kaempferol (Thiede 1994). Though Saint John’s Wort has been observed to inhibit both MAO-A and MAO-B, *Hypericum* extract is a comparatively weak MOA inhibitor (Bladt 1994, Thiede 1994).

The inhibition of the monoamine oxidase enzyme contributes to the efficacy of Saint John’s Wort as an antidepressant. The flavonoid compounds of *Hypericum* extract inhibit MAO in a manner similar to that of the MAOI branch of antidepressant drugs, and thus have the similar effect of preventing monoamine degradation. This increase in available monoamines contributes to the efficacy of *Hypericum* extract as an antidepressant but, as summarized above, Saint John’s Wort is a relatively weak inhibitor of MAO, when compared to MOAI antidepressants. Thus, the antidepressant actions of Saint John’s Wort cannot be described in terms of MAO inhibition alone.

**Saint John’s Wort Inhibition of Monoamine Reuptake**

Once it was realized that MOA inhibition alone could not account for the success of Saint John’s Wort as an antidepressant, it was supposed that *Hypericum* extract might function in a similar manner as the MRI class of antidepressants. It is now widely accepted that the primary mechanism by which *Hypericum* extract acts is through monoamine transporter inhibition.

Early studies with this mindset showed that *Hypericum* extract is in fact a potent inhibitor of neuronal reuptake of 5-HT, NE, and DA (Muller 1996). It has since been found that the phloroglucinol derivative hyperforin (see Figure 4) is greatly responsible for the inhibition of monoamine reuptake exhibited by Saint John’s Wort. Hyperforin is a potent uptake inhibitor of neurotransmitters 5-HT, NE, DA, GABA, and L-Glutamate. It achieves a 50 percent inhibition
rate at concentrations between 0.05-0.10 µg/ml, a potency comparable to that of MRIs currently approved for the treatment of depression in adults and adolescents (Chatterjee 1998). Though there are many other biologically active compounds in Saint John’s Wort that inhibit the reuptake of monoamines, such as adhyperforin and procyanidins (Wonnemann, 2001), hyperforin has been shown to be the most potent inhibitor. It is also the best understood.

![Hyperforin structure](http://en.wikipedia.org/wiki/Hyperforin#/media/File:Hyperforin2DACS.svg)

**Figure 4**

Hyperforin, the monoamine reuptake inhibitor.

Though not all of hyperforin’s ability to inhibit monoamine uptake has been explained, the mechanism by which it inhibits serotonin reuptake has been thoroughly investigated. This MRI mechanism is attributed as providing the main antidepressant action of Saint John’s Wort. Current MRI pharmaceuticals inhibit monoamine neurotransmitter reuptake by blocking the monoamine receptor or by downregulating expression of specific monoamine transport proteins. Hyperforin represents a new mechanism, in that it inhibits 5-HT reuptake by changing the balance of intracellular ion concentrations. Hyperforin activates the nonselective cation channel

Hyperforin’s activation of TRPC6 increases both intracellular [Na⁺] and [Ca²⁺], via an increase in sodium uptake by neurons. The increased sodium uptake effectively leads to a decrease in the sodium gradient that exists between the neuron and the synaptic cleft. Because the activity of SERT is sodium-dependent, the decreased gradient limits transporter action. This results in less 5-HT reuptake, and effectively increases 5-HT concentrations in the synaptic cleft. When this increased monoamine concentration is coupled with hyperforin’s ability to increase the number of 5-HT receptors in the brain in rats (Teufel-Mayer 1997), it greatly accounts for the increased serotonin activity in patients exposed to Hypericum extract. As per the monoamine hypothesis, the increase in monoamine concentrations in the cleft reduces depressive symptoms.

Hyperforin’s action on 5-HT and SERT are by no means the only mechanism by which Hypericum is thought to reduce depressive symptoms. Only more research will elucidate all the manners by which Hypericum extract works to alleviate depression, whether those potential mechanisms correspond to the understanding of depression under the monoamine hypothesis or not. However, hyperforin displays effects on 5-HT reuptake not unlike those of synthetic SSRI antidepressants commonly prescribed to both adults and adolescents. This makes Saint John’s Wort a potential option when choosing between synthetic antidepressants or Hypericum extracts.
Saint John’s Wort as Treatment for Mild to Moderate Depression in Adults

It is important to note that research into Saint John’s Wort has not yet uncovered all the mechanisms by which the plant works to alleviate depressive symptoms. However, enough is known of its mechanism and its efficacy to say that standardized preparations of Saint John’s Wort represent a cost-effective and relatively safe alternative to synthetic antidepressants for patients presenting depressive episodes that are not severe in nature.

Saint John’s Wort is one of the most commonly taken herbal supplements in the world. The plant is prepared in standardized extracts, a variety of which can be found on the market from any number of producers. The active ingredients discussed in the previous two sections, hypericin and hyperforin, represent the most desirable active compounds found in the plant, and pharmaceutical-grade preparations of *Hypericum* emphasize these compounds. Hypericin is standardized from anywhere between .12% and .3% hypericin derivatives. Hyperforin is standardized at concentrations between 1% and 6% (Klemwow). The dosage of *Hypericum* extract is not standardized, due in part because each provider prepares the extract differently. In Germany and many other parts of Europe, Saint John’s Wort is considered a pharmaceutical and as such is subject to strict regulation. Dosages range from 300mg to 600mg or more, but the German Commission E recommends 900mg of standardized extract per day, as delegated by a physician (Klemwow). In the United States, preparations of Saint John’s Wort are considered an herbal supplement by the FDA, and as such they are not subject to the standard scrutiny pharmaceutical drugs must endure to gain approval for use in medicine. As such, the usage of Saint John’s Wort in America is comparatively lower than its use in European countries, a 60 million USD market (Tilburt 2008) compared to a 6 billion USD market (Klemwow).
Cost-wise, Saint John’s Wort is generally significantly less expensive than brand-name pharmaceuticals, and still less expensive than generic options for patients presenting mild to moderate depression. Popular synthetic antidepressants can range in cost between 30 USD a month for low-dose fluoxetine, and upwards of 400 USD a month for something like Fluvoxamine 150mg continuous delivery (Consumer Reports 2013). Saint John’s Wort generally retails for between 10 and 20 USD, where a higher price is correlated with more reliable product, so far as concentrations of the active ingredient are concerned. Taking into account generic options for medications and health insurance, Saint John’s Wort is of comparable price to many other commonly prescribed antidepressants. If a patient does not have access to insurance, however, Hypericum extract can provide a means for treatment that is cost effective.

The efficacy of Saint John’s Wort in the treatment of depression has been demonstrated by numerous studies. A Cochrane Collaboration analysis was performed in 2008 that scrutinized trials which assayed the efficacy of Hypericum extract in treating major depression. A total of 29 clinical trials were analyzed, with a total patient base of 5489 patients. The review found that for larger trials, the response ratio for Hypericum extract versus placebo was 1.28, and for smaller trials that response ratio was 1.87. This led to the conclusion that Hypericum extract was generally superior to placebo in patients with mild to moderately severe depression. Additionally, the review found that response rates for trials comparing Hypericum with tricyclic antidepressants were 1.02, and those comparing Hypericum with MRIs were 1.00. As such, it was deemed that Hypericum extract was similarly effective as standard antidepressants. The analysis also found that patients whose depression was treated with Hypericum extract dropped out of trials due to side effects less often than was the case for tricyclic antidepressants (odds ratio of .24) and SSRIs (odds ratio .53). This led the review to conclude that depressed patients
treated with *Hypericum* extract generally presented fewer severe side effects than those treated with synthetic antidepressants. The results of this review have been debated, as statistical trends as to association of positive outcomes with trail location were observed (Linde). *Hypericum* trials were more successful at reducing depression scores in countries where Saint John’s Wort is approved for treating depression. However, barring a more comprehensive review of the current literature, *Hypericum* extract does seem to be a viable option for the treatment of mild to moderate depressions, comparable in efficacy to some of the currently-available synthetic antidepressants and with less risk of side effects.

Though fewer side effects are associated with Saint John’s Wort than are with MAOI antidepressants and even MRI antidepressants, concerns have been raised as to several dangers which can complicate the use of *Hypericum* extract in the treatment of depression. The most potentially dangerous effect of Saint John’s Wort comes in its ability to react with a wide variety of other medications. Saint John’s Wort is an inducer of transporter P-glycoprotein (P-gp) and several cytochrome P450 (CYP) enzymes (Durr 2000, Madabushi 2006). When the supplement is taken on its own, the increased expression of P-gp and CYP isotopes does little to affect the body adversely. However, many drugs rely on pathways mediated by these metabolic proteins. A patient taking Saint John’s Wort can experience any number of adverse side effects when they combine Saint John’s Wort with any drug mediated by P-gp or CYP (Madabushi).

In America, the status of Saint John’s Wort as an unregulated herbal supplement causes controversy in this regard, in that a patient taking Saint John’s Wort not prescribed by their doctor could make medication decisions that could be deleterious to their health. Generally, it is considered a good idea to treat *Hypericum* extract as one would any other medication by consulting with a physician before starting the supplement. Drug interactions are rare, and
virtually all adverse drug interactions can be avoided if *Hypericum* extract is treated as a medication, rather than as a supplement.

The possibility for adverse drug reactions aside, *Hypericum* extract represents a largely safe approach to the treatment of mild to moderately severe depression in adults. It can be a cost-effective option, and it has been shown to have far fewer side effects than commonly prescribed synthetic antidepressants. In the case of a severe depression, it is unlikely that any physician would recommend Saint John’s Wort over one of the more potent antidepressants that have been studied rigorously over the last three decades. However, in an adult patient presenting mild to moderately severe depressive episodes, Saint John’s Wort represents a good first-option treatment. When recommended by a general practitioner, *Hypericum* extract provides a patient the opportunity to manage their mild to moderately severe depression before consulting with a psychiatrist to consider costlier, side effect-leaden options.
Saint John’s Wort as a Treatment Option for Mild to Moderate Depression in Adolescents

Saint John’s Wort has been shown to act not unlike antidepressants developed and prescribed under the monoamine hypothesis. It is as effective as commonly prescribed monoamine reuptake inhibitors in adults with mild to moderately severe depression, but very little research has gone into determining whether or not extract of *Hypericum perforatum* is suitable for treating adolescents with mild to moderately severe depression. However, there is a clear case to be made for the use of Saint John’s Wort in the treatment of adolescents with depression.

Depression is treated in both adults and adolescents according to the theories set forth in the monoamine hypothesis. As of right now, adolescent treatment methods are adapted from established treatments for adults. The depression that an adolescent experiences, however, is physiologically and pathologically different from that which an adult experiences, due inherent differences in brain chemistry between an adolescent and an adult. This is an important argument to take into account when considering adapting adult treatments to suit adolescent diseases, *Hypericum* extract included. Rat and monkey animal models have shown that both the noradrenergic system and the dopaminergic system mature in late adolescence and early adulthood (Bylund 2007, Wahlstrom 2009). The models also show that the serotonergic system matures much earlier than both the noradrenergic and the dopaminergic systems (Bylund). This could explain why SSRIs seem to be effective in treating both adults and adolescents, while adolescents fail to respond to other classes of MRIs. When considering *Hypericum* extract, it is important to note that hyperforin acts as a potent inhibitor of serotonin reuptake. As such, adapting *Hypericum* extract to treat adolescent depression appears to be supported by animal
models, which confirm that the main antidepressant action of *Hypericum* (serotonin reuptake inhibition) could work in the physiological environment of the adolescent brain.

Indeed, preliminary studies seem to confirm what has been shown in animal models. An open-label pilot study assessing the efficacy of Saint John’s Wort in treating adolescent depression was carried out between 1999 and 2001. Out of 33 patients enrolled, 25 showed significant clinical improvement after 8 weeks of treatment at dosages up to 900mg/day (Findling 2003). A similar 8-week open-label pilot study was published in 2005, in which 9 out of 11 patients who completed the study showed significant improvement in depression scores, based on clinical improvement ratings of very much improved or much improved (Simeon 2005). Both studies suffered from small sample-size, lack of control group, and limited follow-up. However, the positive results obtained confirm that *Hypericum* extract could be effective in treating mild to moderate depression in adolescents. Both pilot studies indicate that controlled trails of Saint John’s Wort in treating adolescent depression are warranted.

Though there is still more to be learned of the mechanisms by which *Hypericum* extract alleviates depression, it functions similarly to MAOIs and MRIs in that it increases the concentration of monoamine available in the brain. While MAOIs are rarely, if ever, prescribed to adolescents because of their harsh side effects and the necessity to follow a strict diet, SSRIs like Fluoxetine are commonly prescribed to adolescents facing depression (TADS). For cases of mild to moderately severe depression where an SSRI might be prescribed, Saint John’s Wort has the potential to perform as well as the synthetic pharmaceutical option, as delineated in the 2008 Cochrane Systemic Review (Linde). Both *Hypericum* extract and commonly prescribed adolescent antidepressants function in accordance to the monoamine hypothesis of depression. Both have the effect of 5-HT reuptake inhibition, which has been shown to be effective in
adolescent animal models. Both the synthetic options and Hypericum extract offer similar results in adults, and only a lack of research appears to be preventing those results from extending to include adolescents. The attractiveness of treating adolescent depression with Saint John’s Wort comes not in that it is more effective at treating depression than are synthetic antidepressants; research has shown that it is at best equivalent to synthetics. The attractiveness of Hypericum extract lies in its low cost and its lack of side effects.

Hypericum extract could provide a level of treatment similar to that provided by common antidepressants, while sparing adolescents from the side effects that come with synthetic options. Side effects attributed to Fluoxetine, which is approved by the FDA for use in children over the age of 8, include nervousness, nausea, dry mouth, sore throat, weakness, loss of appetite, changes in weight, and tremors, among other effects (NIMH 2008). Additionally, adolescents undergoing treatment with antidepressants can experience drastic changes in mood (NIMH 2008). On top of all of that, there is the cultural stigma associated with the use of antidepressant drugs. While they have been deemed safe by the FDA, the notion of putting a child on an antidepressant can be a worrisome thing for a parent or guardian. The black box labels that come with antidepressants, which warn of increased risk of suicide in adolescents, carry a certain terrifying weight with them. Though the risk of adolescent suicide which comes with antidepressants is a debated topic (Bhatia 2007), no doubt the possibility stays on every parent’s mind when they allow their adolescent to obtain antidepressant treatment. That, in combination with the documented side effects of common MRIs, has the potential to ward off adolescents who could require pharmacological intervention to treat their depression.

On the other hand, Saint John’s Wort has few side effects. Side effects may include allergic reactions, restlessness, lethargy, dry mouth, dizziness, and gastrointestinal symptoms
These side effects are rare and transient, and the supplement is widely considered to be well tolerated. Studies have concluded that the safety of Hypericum extract is more favorable than that of synthetic antidepressants, and meta-analysis have indicated that the rate of dropouts from clinical trials due to adverse effects of synthetic antidepressants compared to those of Hypericum extract are 10:1, respectively (Schulz 2006). Instances of severe photosensitivity have occurred in extremely rare cases, and, as noted previously, there is a long list of medications that can react adversely with Saint John’s Wort. However, if taken under the supervision of a physician, drug interactions can be avoided.

The need for more research clearly precludes the recommendation that Saint John’s Wort be used to treat adolescent depression. As mentioned, results of pilot trials assessing Hypericum in treating adolescent depression are promising, and further controlled trials and eventual systematic reviews are warranted. The strongest argument against the use of Hypericum extract is related to concerns over product quality, and rightly so. There have been many investigations and consumer reviews that look into the quality of various Hypericum extracts available on the American market, and results elucidate a complete lack of industry standards. Nearly every aspect of Hypericum extract differs from manufacturer to manufacturer. An analysis of 54 of the top-selling Hypericum extracts was undertaken by Draves and associates in 2003. Supplements were assessed on the basis of naphthodianthrone content, which is marketed to consumers as an insurance of quality control. They found that the actual concentrations of hypericin contained across all products ranged between 0% and 108.62% of labelled concentrations. Only 2 of the 54 supplements were confirmed to contain naphthodianthrone concentrations within 10% of their label claims (Draves 2003). Furthermore, the study emphasizes the fact that the Hypericum extract industry in the United States does not even advertise their product based on the confirmed
main-source of antidepressant action in Saint John’s Wort. Products make claims about hypericin and psuedohypericin content, but usually forgo advertising hyperforin content altogether.

These results are distressing on multiple levels. The extreme range of active ingredient concentrations found across all samples, and the false manufacturer’s claims as to the actual potency of the supplements, means that recommending common American Saint John’s Wort preparations for adolescent depression is unwise. Until a set of federally-standardized regulations is put into place governing hyperforin content and manufacturer’s claims, Saint John’s Wort extracts produced or marketed specifically in America should be regarded as a poor choice for the treatment of any depression, let alone adolescent depression. However, it is not necessarily difficult to obtain quality *Hypericum* extracts. In Germany, *Hypericum* extract is prescribed by physicians and approved by the Commission E as a treatment for mild to moderate depression. Physicians rightly recommend *Hypericum* extract that is standardized for hyperforin, rather than naphthodianthrones (Kelmwow), and manufacturers are held to standards when labelling their products. Just as all currently prescribed antidepressants have been standardized and regulated by the FDA, so too must Saint John’s Wort be regulated. However, as it stands right now, this responsibility would fall solely on the prescribing physician, whose job it would be to make sure the product they endorse is a quality one. Quality *Hypericum* extracts are widely available on web-based marketplaces, and all it would take to prevent ineffective treatment would be guidance in choosing reputable brands. By avoiding products that haven’t been regulated by governmental agencies, such as the Commission E, the quality-control concerns over Saint John’s Wort can be eliminated.

*Hypericum* extract represents a desirable candidate for the treatment of mild to moderately severe depression in adolescents. It provides clinically proven alleviation of
depressive symptoms in adults that could, based on the current theories governing treatment, extend well to adolescents. It provides a treatment option largely bereft of severe side effects that, when taken under the care of a trained physician, poses little danger in the way of drug interactions. It is cost-effective when compared to the prices of commonly prescribed antidepressants, and it carries perhaps less of a stigma than do the black box labelled antidepressants currently marketed for use by adolescents.
Conclusion

Though a good case can be made for *Hypericum perforatum* as an attractive treatment option in mild to moderately severe adolescent depression, the bottom line is that more research must be undertaken before anything can be certain. Very little research has gone into determining how *Hypericum* extract interacts with the depression of an adolescent mind, and researchers are just beginning to understand the way in which hypericin, hyperforin, and the other biologically active compounds of Saint John’s Wort work to alleviate depression. There is clear research which says that *Hypericum* extract is an effective treatment option when considering mild to moderate depression in adults, and pilot studies indicate efficacy in treating adolescent depression. Because *Hypericum* works on the same systems to achieve the same results as currently approved adolescent antidepressants, it would appear that *Hypericum* extract, could very well treat mild to moderately severe depression in adolescents, with the added benefits of increased tolerability and decreased cost. Common concerns as to quality-control of the supplement can be eliminated by avoiding unregulated products. If further research were to be carried out that looks into the efficacy of Saint John’s Wort in adolescents, it could open up the door for a potential first-line treatment option for adolescents suffering from depression.

It is not the goal of this paper to review the current literature and suggest that *Hypericum* extract be approved by the FDA and used as a main form of treatment for adolescents suffering with mild to moderately severe depression. Rather, Saint John’s Wort has the ability to occupy a unique niche in the treatment of depression, in that it offers a less severe, less expensive form of treatment. Regulated, hyperforin-standardized *Hypericum* extracts such as those found in Germany would appear to be a good option for a first line of pharmacological treatment when considering an antidepressant for adolescents. Research has shown that it is by no means the
most powerful antidepressant on the market, and so by no means should it be a first choice for an adolescent presenting severe depressive episodes. However, in the case of an adolescent who is just recognizing their mild or moderate depression, *Hypericum* extract would offer the potential for decreased depressive symptoms, and the potential to alleviate the depression before it progresses into something more severe, all without relying on the stigmatized and side effect-laden synthetic antidepressant options.
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