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The Side Effects of Antidepressants and the Importance of Medicinal Plants in the Treatment of Depression

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Abstract

Depression is an incapacitating psychiatric ailment which is characterized by a pervasive low mood, loss of interest in daily activities, diminished ability to experience pleasure (anhedonia), withdrawal of interest, feelings of worthlessness, and suicidal tendencies. It is estimated that by the year 2020 if current trends continue, the burden of depression will increase to 5.7% of the total burden of disease and it would be the second leading cause of disability-adjusted life years. Many synthetic antidepressant drugs used in depression treatment show low response rates and even produce adverse/side-effects such as cardiotoxicity, sexual dysfunction, and sleep disorder, in depressed patients. Therefore, it is desirable to seek antidepressants in medicinal plants; such materials are expected to show fewer side-effects. In this review we evaluated the side effects of antidepressants and emphasized the importance of medicinal plants in the treatment of depression

Keywords: Antidepressants, The Side Effects Of Antidepressants, Medicinal Plants

Introduction

Depression is a psychiatric disorder which is characterized by symptoms such as sadness, despair, feeling of worthlessness, impaired bodily functions (such as sleep, appetite or sexual interest), loss of interest in living, and suicidal tendencies (Schechter et al., 2005). Affecting 15% of the population throughout their lifetime and 5% during the last year in developed countries, depression continues to become a greater problem each day both for individuals and the community, and is estimated by the World Health Organization to become the second disorder to adversely affect the human life after cardiovascular disorder by 2020 (Murray & Lopez, 1997, Bromet et al., 2011). Depression is a common psychiatric disorder which can develop at any age, and studies demonstrated that its lifetime prevalence ranges from 1.5% to 19% (Olchanski et al., 2013). Its prevalence varies largely between genders, 5-12% in men and 10-25% in women (Klose & Jacobi, 2004). Depression is more prevalent in unemployed, divorced, widowed or separated individuals (Ohayon et al., 1999). The rates of depression vary in different countries of the world, being 3.6% in South Korea, 1.7-2.5% in China and 2.2% in Ethiopia, and it has been reported that the prevalence is increased in poorly educated individuals (Demyttenaere et al., 2004, Ohayon & Hong, 2006, Fekadu et al., 2007). Although many hypotheses have been proposed to elucidate the etiology and physiopathology of depression, none of these alone could

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explain depression. It has been emphasized that individual predisposition, genetic and environmental factors, and neurophysiological and neurochemical parameters may induce depression (Duman et al., 2000).

One of the most important problems encountered in the treatment of depression is discontinuation of the drug by the patient because of side effects. This is one of the most important causes of treatment failure and has increased to significant levels. Studies showed that approximately 43% of patients stop using or do not regularly use their drugs because of adverse effects (Bull et al., 2002). This accelerated the efforts to develop new drugs that can be used in the treatment of depression, and The Food and Drug Administration (FDA) has recently approved three new antidepressants i.e vilazodone, levomilnacipran and vortioxetine (Zhang et al., 2015, Meeker et al., 2015, Asnis & Henderson, 2015). Efforts to develop drugs that are expected to show antidepressant activity with less side effects are continuing, and side effects that lead to failure of antidepressant treatment are summarized in table 1.

Table 1. Some undesirable side effects of antidepressants

- Cardiovascular side effects: Orthostatic hypotension, hypertension, QT prolongation, rhythm disturbances.
- Gastrointestinal side effects: Abdominal pain, nausea, GI hemorrhage, vomiting, diarrhea.
- Sexual dysfunction
- Side effects on the CNS: Reduced seizure threshold, extrapyramidal side effects, headache, stroke, serotonin syndrome.
- Metabolic disorders: Weight gain, diabetes
- Risk of hemorrhage
- Increased suicidal tendency and high-dose drug use
- Sleep disorders
- Mood disorders
- Effects on the genitourinary system and hyponatremia
- Hyperprolactinemia
- Sweating
- Ophthalmic side effects
- Osteoporosis and bone cracks
- Hepatotoxicity
- Risk of malignancy

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- Hypersensitivity reactions
- Withdrawal symptoms and abstinence syndrome
- Risks of use during pregnancy

Cardiovascular Side Effects

Orthostatic hypotension is a common side effect associated with the use of antidepressants. This effect occurs mainly due to the α1-adrenergic receptor activity of trisiclic antidepressants (TSA) group of drugs, but is also seen with selective serotonin reuptake inhibitors (SSRI) and serotonin–norepinephrine reuptake inhibitors (SNRI) groups. Orthostatic hypotension is commonly seen with paroxetine, which is a member of the SSRI group, and it is thought that this effect is a result of the anticholinergic property of the drug (Darowski et al., 2009, Rodriguez de la Torre et al., 2001). SNRI drugs such as duloxetine may increase blood pressure (Thase et al., 2005). QT prolongation associated with the use of SSRIs is a common condition in clinical practice (Funk & Bostwick, 2013).

After observing that the use of TSAs in clinical practice leads to serious cardiovascular side effects, these side effects have been significantly reduced with newly drugs such as SSRIs. While they have a safer side effect profile with less anticholinergic effects, cardiovascular side effects such as changes in cardiac rhythm have been reported with this group of drugs. Limited data is available on the cardiovascular side effects of new antidepressants such as levomilnacipran, and it is thought that they may cause increased cardiac rhythm due to their noradrenergic effects (Pacher et al., 1999, Zhang et al., 2015).

Gastrointestinal Side Effects

It has been suggested that the major factor that mediates the gastrointestinal (GI) side effects of antidepressants that often manifest themselves as nausea and vomiting is serotonin, and central 5-HT3 receptors play and important role in such effects (Janssen et al., 2010). Abdominal pain, diarrhea and GI hemorrhage are the other GI side effects of antidepressants, and among SSRIs, fluvoxamine is associated with the highest rate of GI side effects whereas escitalopram is less likely to cause GI side effects (Spigset, 1999). Another study demonstrated that venlafaxine causes more nausea and vomiting than duloxetine and SSRIs, and sertraline may be a good option even with respect to such side effects (Gartlehner et al., 2011). Use of non-steroidal anti-inflammatory (NSAI) drugs is one of the major causes that increase the risk of GI hemorrhage (Spigset, 1999). Limited studies have been conducted on the GI effects of drugs such as vilazodone, levomilnacipran and vortioxetine that have been recently approved by FDA, and it has been reported that similarly to other antidepressants, nausea and vomiting are commonly seen with these drugs (Zhang et al., 2015, Meeker et al., 2015, Asnis & Henderson, 2015).

Risk of Hemorrhage

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Any antidepressant acting on the serotonergic system cause increased bleeding tendency through various mechanisms. Reduction of platelet levels through serotonin reuptake inhibition is prominent among these mechanisms, and sertraline, paroxetine and fluoxetine are those which mostly increase bleeding tendency among SSRIs that show this side effect. The risk of hemorrhage increases in cases of multidrug use; and GI bleeding tendency increases especially when NSAI drugs are used in combination with SSRI antidepressants (Spigset, 1999, Andrade et al., 2010).

Sexual Dysfunction

The prevalence of sexual dysfunction is significantly higher in patients with major depression than in the normal population. Loss of libido has been reported in 25-75% of patients with major depression, however sexual dysfunction are also seen as a side effect of antidepressants. The prevalence of these side effects in patients on SSRIs is about 50-70%, and similar side effects are also seen with SNRIs. The rates are lower with drugs acting through dopamine or noradrenalin. To solve this problem, which poses a major obstacle to the treatment of depression, patients should be monitored for side effects and if needed, drugs showing less sexual side effects such as bupropion, agomelatine or mirtazapine should be considered as alternatives (Williams & Reynolds, 2006, Bella & Shamloul, 2014, Reichenpfader et al., 2014).

Side Effects on the Central Nervous System

Antidepressants should be used with caution in epileptic patients since they lower the seizure threshold (Haddad & Dursun, 2008). Moreover, especially antidepressants acting on the serotonergic system are known to cause extrapyramidal side effects which have been suggested to be mediated by the effect of increased serotonin levels on the dopaminergic system (Hawthorne & Caley, 2015).

Another problem that results from increased serotonin levels and can be life-treatening is serotonin syndrome. To avoid serotonin syndrome which mostly develops with combined use of SSRIs with MAO inhibitors, drugs should be chosen with caution (Iqbal et al., 2012). Headache is seen as a side effect of many antidepressants, and there are studies which demonstrated that SSRIs increase the risk of stroke (Fava et al., 2006, Anderson et al., 2012).

Metabolic Disorders

Weight gain is a common side effect of many antidepressants, and it has been suggested that its mechanism of action is multifactorial. Changes in the appetite of the patient, the body's reduced calorie burning due to the sedative effect of some antidepressants, the effect of some specific histaminergic and serotonergic neuroreceptors, changes in food preferences, and increased food and drink consumption due to xerostomia which is a side effect of many antidepressants are the factors that lead to weight gain. Among SSRIs paroxetine leads to most weight gain, and another drug with which this effect is frequently seen, mirtazapine, causes weight gain more commonly at the beginning of the treatment. Weight gain is a side effect of antidepressants, but it should be

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noted that also depression can lead to weight gain (Serretti & Mandelli, 2010, Zimmermann et al., 2003). On the other hand, some antidepressants are known to cause weight loss, and it was reported that weight loss is seen in patients on venlafaxine, which is similar to sibutramine in structure, and similar results were obtained in a study with bupropion (Gadde et al., 2001, Silverstone & Ravindran, 1999). It has also been suggested that antidepressants can change serum lipid parameters and increase the risk of diabetes (McIntyre et al., 2006, Bhattacharjee et al., 2013).

Increased Suicidal Tendency and High-Dose Drug Use

Because suicidal tendency has become a serious problem especially in children and adolescents using antidepressants FDA requires a black box warning on drugs for these patient groups since 2014 (Stone, 2014). While suicidal tendency is known to be a problem in children and adolescents, this is controversial in adults (Braun et al., 2016). Suicidal thought is common in mood disorders, and a study reported that 12% of individuals with obsessive-compulsive disorder have suicidal thoughts (Storch et al., 2017). Since association of antidepressants with suicidal tendency brings the risk of suicidal attempt through use of these drugs at high doses, safety of using the drugs at high doses has come under question. In a study, it was reported that the antidepressant group with the highest fatality rate if taken at high doses is TSAs, followed by venlafaxine and mirtazapine, while the safest group is SSRIs. This study also reported that among SSRIs citalopram has the highest rate (Hawton et al., 2010).

Sleep Disorders

Studies demonstrated that venlafaxine and SSRIs increase the duration of REM sleep periods and shorten the total REM phase during sleep. This condition that occurs during the first weeks of the treatment and usually returns to normal limits after 8 weeks of treatment is thought to be associated with increased serotonin levels in the synaptic cleft. Since it is known that mirtazapine also increases the duration of REM sleep periods, mirtazapine and trazodone have been found beneficial for sleep disorders in patients with major depression (Wilson & Argyropoulos, 2005). Restlessness and nightmares have been reported in patients initiating treatment with SSRIs and SNRIs (Tribl et al., 2013).

Mood Disorders

Various mood disorders, i.e agitation, panic attack disorders, nervousness, restlessness, sleepiness, anxiety, irritability and aggression have been reported to develop especially during the first three weeks of antidepressant treatment (Harada et al., 2008).

Effects on the Genitourinary System and Hyponatremia

Many antidepressants, mainly SSRIs and SNRIs, cause urinary retention. It is thought that increased serotonin levels caused by these drugs leading to activation of central sympathetic system and inhibition of parasympathetic system affects the central micturition pathways may cause urinary retention, and that antidepressants may show this effect through α1-adenoreceptors

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(Thor, 2003, Votolato et al., 2000). It has been suggested that antidepressants can cause hyponatremia by affecting secretion of antidiuretic hormone (ADH) or causing changes in ADH sensitivity. While hyponatremia is more common in patients receiving SSRIs and the use of diuretics increase the risk of occurrence of this side effect, mirtazapine, TSA ve SNRIs can be preferred in case of hyponatremia since this side effect is less common with these drugs (De Picker et al., 2014).

Hyperprolactinemia

The secretion of prolactin hormone, which is produced in the pituitary gland, plays a role in the milk production during lactation, and shows a number of effects such as menopause and ovulation is controlled by dopaminergic pathways. Since these pathways are indirectly affected by serotonin through 5-HT1c and 5-HT2 receptors, hyperprolactinemia may occur as a side effect of antidepressants. Regular monitoring of prolactin levels is not necessary in such cases, but serum prolactin levels should be measured and the antidepressant should be changed as needed if symptomatic findings are present. Mirtazapine is an alternative option, or switching to another SSRI may normalize the hormone levels (Rittenhouse et al., 1993, Mondal et al., 2013).

Sweating

Sweating is a mechanism that the body uses to maintain normal physiological temperature, but hyperhidrosis (excessive sweating) that occurs as a side effect of many antidepressants disturbs the patients and causes discomfort in social situations. Hyperhidrosis resulting from the effect of TSAs on the muscarinic receptors affects 14% of patients who use these drugs. Among new generation antidepressants, bupropion and venlafaxine similarly cause hyperhidrosis while it has been reported that this side effect is less common with fluvoxamine and trazodone (Trindade et al., 1998, Marcy & Britton, 2005).

Ophthalmic Side Effects

Studies with SSRIs demonstrated that these group of drugs can cause narrow-angle glaucoma by increasing the intraocular pressure (Costagliola et al., 2004). Similar side effects have also been observed with venlafaxine and bupropion, and ophthalmic side effects are not limited to these; findings have been reported indicating that fluvoxamine, paroxetine and venlafaxine, which are new generation antidepressants, increase the risk of cataract (Etminan et al., 2010, Ng et al., 2002, Symes et al., 2015).

Osteoporosis and Bone Cracks

It has been shown that the risk of osteoporosis, bone cracks and fractures is increased in patients treated with antidepressants. It has been suggested that this is a result of increased cortisone levels due to impaired HPA axis. It is still not clear whether such cases seen in patients with depression result from the use of antidepressants or from depression or both (Cizza et al., 2009).

Hepatotoxicity

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Another problem associated with chronic use of antidepressants is hepatotoxicity. This condition, developed in 0.5-1% of patients treated with SSRIs and SNRIs, is more common in those who use nefazodone, agomelatine and bupropion while citalopram and escitalopram are considered safe in terms of hepatotoxicity. Hepatotoxicity may develop as late as six months, but may also be seen within a few days after initiation of the drug. It may be life-threatening in some cases; in fact, toxicity cases requiring liver transplantation have been reported associated with the use of agomelatine, venlafaxine, duloxetine and nefazodone. ALT levels increased to three times the normal values is an important clinical indicator of hepatotoxicity associated with drug use. Asthenia and loss of appetite are observed associated with the development of hepatotoxicity. It is dose-dependent, and the risk further increases with high doses. Moreover, use of more than one antidepressants is another factor that increases the risk of hepatotoxicity if there is metabolism by the same isoenzyme of CYP450 in multidrug use (Voican et al., 2014, Chen et al., 2013).

Risk of Malignancy

Some pre-clinical studies suggested that antidepressants can accelerate development of fibrocarcinoma, melanoma and breast cancer while some experimental studies showed totally opposite results demonstrating the protective effect of these drugs on tumor models. In summary, the effects of antidepressants on the risk of cancer is a question of debate and studies are ongoing on this issue (Brandes et al., 1992, Gil-Ad et al., 2008, Abdul et al., 1995).

Hypersensitivity Reactions

It has been reported that antidepressants, mainly SSRIs, can cause cutaneous reactions, and the risk of development of this adverse effect may further increase with exposure to sunlight. Long-term use of SSRIs can lead to hyperpigmentation in the skin, hair and nails, and complaints such as redness, acne, dermatitis and hair loss have been reported in patients using mirtazapine (Mitkov et al., 2014).

Withdrawal Symptoms and Abstinence Syndrome

Another problem seen in the treatment depression is symptoms of withdrawal and abstinence that develop upon discontinuation of the drug at the end of the treatment. These include: tremor, tachycardia, flu-like symptoms, shock-like feelings, paresthesia, myalgia, neuralgia, tinnitus, ataxia, vertigo, sexual dysfunction, sleep disorders, nausea, vomiting, diarrhea, anxiety and various mental disorders. To reduce or prevent such symptoms, tapering off the dose gradually may be useful (Wilson & Lader, 2015, Fava et al., 2015).

Risks of Use During Pregnancy

The risk of development of depressive disorders increase during pregnancy, and it is known that 10-15% of pregnant women develop depression during pregnancy. The risk of depression is at the highest level during the second and third trimesters, and depression persists until the end of pregnancy in about half of the patients with depression (Bennett et al., 2004). Since

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preeclampsia, premature birth, abnormal bleedings and spontaneous abortions are associated with complications of pregnancy, treatment of depression is very important during pregnancy (Grigoriadis, VonderPorten, Mamisashvili, Tomlinson, et al., 2013). Drug therapy is a point that should be taken into consideration during pregnancy, because studies have demonstrated the harmful effects of many antidepressants during this period. It has been reported that SSRIs can cause pulmonary hypertension during pregnancy, paroxetine is associated with congenital cardiac defects, SNRIs can increase post-partum bleeding, and venlafaxine can cause hypertension during pregnancy (Grigoriadis, VonderPorten, Mamisashvili, Roerecke, et al., 2013, Grigoriadis et al., 2014, Furu et al., 2015, Bellantuono et al., 2015). Decision about using antidepressants during pregnancy is made based on the physician's evaluation of the the benefits and risks of a drug. The grade and possible underlying causes of depression are evaluated, and for stable patients who are already receiving drug therapy it is usually recommended to continue the current therapy if they do not receive drugs with serious risks such as paroxetine. If the patient does not use any drug and will start treatment, it is recommended to initiate the treatment with a drug such as sertraline or citalopram (Larsen et al., 2015).

In clinical practice, decreased patient compliance due to the side effects of antidepressants is one of the most important causes of failure of the treatment of depression (Brunello et al., 2002, MacGillivray et al., 2003). Newly developed synthetic antidepressants could not provide significant improvement in terms of side effects; the three antidepressants (i.e vilazodone, levomilnacipran and vortioxetine) recently approved by FDA have been reported to show similar side effects to the older synthetic antidepressants (Zhang et al., 2015, Meeker et al., 2015, Asnis & Henderson, 2015). Novel treatment options by ketamine have difficulties such as patient compliance, on the other hand, drug abuse or dependence problem for opioid agonists have not been solved yet (Ceskova & Silhan, 2018). The patients' inability to tolerate or rejection to use the drug because of side effects, poor response to the treatment, disagreement to use antidepressants because of social and cultural reasons, and the economic burden caused by synthetic antidepressants are some of the common challenges in the treatment of depression (Barnes et al., 2004). All these increase the importance of complementary therapy methods that show less side effects. Therefore investigation of medicinal plants that are expected to show less side effects in the antidepressant treatment have become necessary. Starting from this point of view, many studies were conducted to investigate the antidepressant effects of medicinal plants, some of them are listed on table 2 (Rabiei & Rabiei, 2017). Medicinal plants examined with respect to possible use in the treatment of depression can be used for therapeutic purposes and also as an adjuvant therapy to improve the efficacy of the current therapy or to reduce the side effects of a synthetic drug. For example, lavandula tincture improves the antidepressant effect of imipramine, it has been demonstrated that Ginkgo biloba extract reduces the brain damage caused by venlafaxine in rats, and addition of Passiflora incarnata plant extract to the therapy with Hipericum perforatum improves the antidepressant efficacy (Akhondzadeh et al., 2003, Qin et al., 2005, Fiebich et al., 2011). Since studies have demonstrated that about 30% of patients with depression do not respond to monotherapy, combined therapy options have become important (Papakostas et al., 2008). With the combined therapy strategies that are especially important in treatment-resistant depression, it is aimed to improve the therapeutic effect with less

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side effects and to reduce the withdrawal symptoms of the drugs (Lam et al., 2002). However, serious risks such as serotonin syndrome are among the major obstructions to the use of combined drug therapies (Iqbal et al., 2012). On the other hand, there are studies in which synthetic drugs and plants were used in combinations (Qin et al., 2005). A clinical study demonstrated that when used in combination lavandula tincture improves the antidepressant effect of imipramine and decreases the time to onset of the favorable effects of the therapy, reduces the anticholinergic side effects, but increases the complaints of headache (Akhondzadeh et al., 2003). In another clinical study, crocin capsules obtained from Crocussativus (crocus) stigmae were given for 4 weeks to patients with major depresssion who were being treated with fluoxetine, sertraline or citalopram, and it was shown based on BDI, GHQ and BAI assessments that crocin improves the therapeutic effect of each of the three antidepressants (Talaei et al., 2015).

It has been suggested that oxidative stress contributes to the physiopathology of depression. Oxidative stress is known to cause some disorders, especially DNA damage and also telomer shortening and endothelial dysfunctions. It has been reported that the DNA damage in the blood of patients with bipolar disorder correlates with the disease symptoms (Andreazza et al., 2007). It has been shown that antioxidant parameters such as SOD, MDA, CAT and nitric oxide are impaired by oxidative stress in patients with depression, and favorable effects of antioxidants on the symptoms of depression have been demonstrated by some clinical studies. It has been reported that N-acetylcysteine improves depressive symptoms in patients with bipolar disorder (Berk et al., 2008, Ozcan et al., 2004). Also there are studies that demonstrated that combined use of antioxidants and synthetic antidepressants may improve the therapeutic effects and reduce the side effects. For example, N-acetylcysteine improves the therapeutic efficacy of fluvoxamine in the treatment of patients with obbessive-compulsive disorder (Qin et al., 2005, Lafleur et al., 2006). Likewise some of medicinal plants are thought to show their antidepressant activity due to their antioxidant properties (Herraiz & Guillen, 2018). Although the exact mechanism by which antioxidants show antidepressant activity is not known, their effect to increase the serotonin and noradrenalin levels in the synaptic cleft similarly to synthetic antidepressants or inhibition of monoamine oxidase may play a role (Bouayed & Bohn, 2010, Herraiz & Guillen, 2018)

Table 2. Some of medicinal plants having antidepressant activity

Medicinal Plant	**Family**	**Parts used**	**Extract**
Foeniculum Vulgare	Apiaceae	Fruits	Methanolic
Eugena caryophyllus	Myrtaceae	Flower bud	Aqueous
Rosmarinus officinalis	Labiatae	Fresh juice	Hydroalcoholic
Magnolia bark	Magnoliaceae	Bark	Ethanolic

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Zingiber officinale	Zingiberaceae	Rhizome	Ethanolic
Valeriana officinalis	Caprifoliaceae	Roots	Ethanolic
Crocus sativus	Iridaceae	Petals	Aqueous
Gingko biloba	Ginkgoaceae	Leaves	Lipophilic
Allium cepa	Liliaceae	Bulb powder	Aqueous
Curcuma longa	Zingiberaceae	Root and rhizome	Aqueous
Albizza julibrissin	Fabaceae	Bark	Ethanolic
Gentiana kochiana	Gentianaceae	Aerial part	Diethylether
Cassia occidentalis	Caesalpiniaceae	Leaves	Ethanolic and aqueous
Areca catechu	Arecaceae	Nut	Ethanolic
Salvia elegans	Lamiaceae	Leaves	Hydroalcoholic
Piper laetispicum	Piperaceae	Stem and root	Ethyl acetate
Hypericum canariense	Hypericaceae	Aerial part	Methanolic
Lafoensia pacari	Lythraceae	Leaves	Ethanolic
Asparagus recemosu	Asparagaceae	Seeds	Methanolic
Jasminum sambac	Oleaceae	Leaves	Methanolic

Discussion

Numerous in vitro, pre-clinical and clinical studies were conducted with medicinal plants for depression. While in-vitro studies give an idea about the pharmacological effect of a plant, the effect of the in-vivo metabolism and pharmacokinetic parameters should not be ignored, and in-vitro studies should be supported by in-vivo findings. For many plants, no data is available on the clinical use while antidepressant activity has been shown in in vitro studies and with experimental animal models. When the clinical studies conducted in order for herbal drugs can be used effectively and safely are reviewed, it is seen that the data obtained is insufficient. We believe that St. John's Wort (H. Perfaratum) should be evaluated separately from other plants when using this approach; because studies with this plant provide important data about issues such as the dose to be used, indications, side effects and interactions about the herbal drug (Linde et al., 2008). However, further clinical studies are warranted in order for medicinal plants in general can be used in the treatment of depression. Additionally, we believe that it is important to evaluate medicinal plants similarly to drugs and investigate them for diseases, drug and food interactions, for adverse effects and for toxicity in order for they can be used safely in clinical practice.

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Conclusion:

Since failures of or inadequate response to the treatment of depression may be seen due to the side effects of drugs, new therapeutic approaches to the treatment of depression are needed. Studies with medicinal plants that are expected to show less side effects are valuable especially in this respect, and in order for these can be used in the treatment of depression, further clinical studies are warranted. Since results of studies may be affected by many factors such as the geographical location where the plant grows, the season it is collected, the properties of the soil in which it grows, the part used, drying technique, humidity and air temperature; the isolation and standardization of the active substance responsible for the pharmacological effect is important. We believe that standardization and introduction as appropriate pharmaceutical formulations of medicinal plants of which the efficacy and safety has been proven will provide important contributions to science and humanity.

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