

**The prescription and rationale for the use of herbal medicines
by psychiatrists in Karaj city, Iran in the treatment of
depression**

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October 2022

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Abstract

Background and Objectives: Depression is a deadly and debilitating disorder that has progressed rapidly in human societies, so effective treatments with fewer complications are needed. This disorder has different types and can be divided into major depressive disorder (including major depressive episode), persistent depressive disorders (dysthymia), DMDD or disruptive mood dysregulation disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, and other specified and unspecified depressive disorders. Depression cannot be considered a single disease because it can be a sign of many biological processes that are out of balance. Among the various treatments for depression, the use of synthetic drugs can be considered as the first line of treatment, although they do not help all patients and have their own side effects and can cause many problems. Since the general popularity of traditional medicine in Iran has become more widespread today and many herbs have been used for various purposes in the past, including depression, it may be good to explore the use of herbal medicines as new therapeutic approaches. Therefore, this article has explored anti-depressant herbal medicines available in Iran and using a questionnaire to examine the approach of psychiatrists in Karaj to herbal medicines in the treatment of depression.

Method: The review section of this article is based on clinical trials and drugs introduced by pharmaceutical companies in Iran, and the second part (Chapter 3) of this article is related to statistical data and the results of interviews with psychiatrists. Communication with psychiatrists (25% of all psychiatrists in Karaj) has been done both in person and through social media (Instagram).

Results: According to the available research, effective herbal anti-depressants available in Iran are Hypiran, Perforan, Nervoxin, Rose oral drop, Rocina, SaffroMood, Cephalum Urtica, Deproherb drop and capsule, Epion, Simosleep tablet, Lavender syrupe, Ginkogol and Ginkgo TD tablets and GinSin capsule that often used to treat mild to moderate depression (not in severe cases). Among these drugs, Nervoxin, Perforan, Simosleep, Ginkogol, Ginkgo TD, SaffroMood and Ginsin are prescribed by some psychiatrists in Karaj, but most psychiatrists prefer to use synthetic drugs.

Conclusion: According to the results of the data of this article, it seems that herbal medicines are used in treating mild to moderate depression and with relatively few side effects. In most cases they are used as adjunct therapy. In the city of Karaj, Iran, 70% of psychiatrists use synthetic drugs and only 30% use herbal anti-depressants as occasional adjunctive therapy.

Key words: Depression, anti-depressant, Karaj city, Psychiatrist, Herbal anti-depressants, Hypiran, Perforan, Nervoxin, Rose oral drop, Rocina, SaffroMood, Cephalum Urtica, Deproherb drop and capsule, Epion, Simosleep tablet, Lavender syrupe, Ginkogol, Ginkgo TD tablets, GinSin capsule

Introduction and Method

Depression is very common and potentially fatal disease. People can experience joys and longings every day, but when their mood disorders interfere with daily activities and reach a point of clinical significance, they may be diagnosed with depressive disorder. Various definitions and causes for depression have been proposed. We now know that depression can have many types and causes and be associated with biochemical, cognitive-behavioral and psychological changes, but what is significant is the timely diagnosis and selection of an appropriate treatment for this disease. It seems that among the various treatments for depression, synthetic drugs are used as the standard treatment for depressed patients, but at the same time they have side effects such as initial worsening of mood, GI, sexual dysfunction, dry mouth, sleep disorders, blurred vision, weight increase, that can be significant. For centuries, people around the world have been using herbs to treat their anxiety and depression, such as saffron, valerian, lemon balm, and the like. As the incidence of depression may increase with the advent of the Corona virus and reduced communication, the use of herbal remedies may be needed more than ever and could open the door to relieve symptoms for many people with the disease. This article focuses on herbal antidepressants available in Iran and examines the effects of these herbal medicines on depression.

In order to discover herbal anti-depressant drugs believed to be effective in Iran, we looked at those available in Iranian pharmacies and pharmaceutical companies. Fourteen anti-depressant herbal medicines were found. The herbs included in these medicines were then examined and various clinical trials were reviewed on the antidepressant properties of these herbs. The prescription of some of these drugs by psychiatrists also suggests that the obtained herbal drugs may be effective in the treatment of depression.

In order to locate psychiatrists, that might be available for interview, the website of Karaj Medical System. Of those psychiatrists who visited online and were residents of Karaj, 80 psychiatrists were found in Karaj, and 25% of them were interviewed. In this research, psychiatrists of all ages, male and female, living in Karaj with doctorate or post-doctorate degrees were interviewed in places such as four-way Taleghani, Azimieh, Mehrshahr, Jahanshahr, Golshahr and Shahin Vila. Due to the existence of some limitations, such as the reluctance of psychiatrists to participate in research work, or the lack of time for face-to-face interviews, most of the interviews were conducted offline and through Instagram, and a limited number were also conducted in person.

Chapter 1: Depression

Depression is a mood disorder that is associated with feelings of sadness and lack of motivation and pleasure, and it can affect the quality of a person's life, and it seems that depression has become a part of modern life. Depression can have different symptoms and definitions based on its different types. In this chapter, the history of depression, its causes, epidemiology and its different types are discussed according to the diagnostic and statistical manual of mental disorders (DSM-5) criteria.

1.1 History

In the past, major depressive disorder was known as melancholia. At the time, Hippocrates, a Greek physician, stated that the disease was caused by an imbalance in four body fluids (including yellow bile, black bile, sputum, and blood), and that Hippocrates' selective treatment included taking blood, bathing, and exercise. Eventually different types of melancholy were suggested, and alternative terms were suggested and discarded. The term depression was finally in the modern sense coined in 1665. In the twentieth century, the German psychiatrist Emile Kraepelin was the first to diagnose manic depression. Also, in the late 1920s, there were many discussions between psychiatrists on the types of depression and their possible causes.¹

Many psychologists have offered various definitions and reasons for depression, until in the mid to late twentieth century, researchers theorized that depression was caused by a chemical imbalance in neurotransmitters in the brain.¹

1.2 Epidemiology

The United Nations World Health Organization (WHO) reports that depression is a major cause of disability and is estimated to affect more than 300 million people worldwide (especially women, young people and the elderly). WHO ranks depression as the fourth leading cause of disability worldwide. All epidemiological studies also suggest that gender, age, and marital status are associated with depression, but the extent of these relationships varies in different cultures and countries. Demographic studies have shown that major depression is reported twice as often in women as in men, although it is not clear why. Depression seems to be more related to psychosocial factors than hormonal factors. It also seems that the prevalence of depression is higher in people who are separated or divorced than in married people. Major depression can

occur at any age, but it increases with age. Although it seems that inappropriate social situation, weak economic situation and low income can play a role in causing depression. But on another level, since people in high-income countries may experience more stress than in low-income countries, or income inequality is more common in these rich countries, a wide range of depression can also result. Therefore, more investigations and studies are needed regarding the relative influence of factors involved in the development of depression, but it should also be considered that the factors involved can affect depression in different ways in different cultures and countries.² It should also be noted that the prevalence of depression has increased significantly with the epidemic of the Covid-19 virus in recent years.³

1.3 Etiology

In general, the causes of depression can be divided into three categories: biological, psychological and socio-cultural. The table below shows these divisions with the subgroups of each category.⁴

Biological perspective	Inheritance (Major depressive disorder has a hereditary rate of 37% and bipolar depressive disorder has a hereditary rate of 60% to 85%)
	Probably biochemical abnormalities (changes in the levels of neurotransmitters such as serotonin, norepinephrine and dopamine)
	Medications (such as birth control pills, sleeping pills, etc.)
Socio-cultural perspective	Stressors such as: Sexual abuse, Poverty, Single parenthood, Periodic stress such as burnout, Job loss, etc.

Psychological perspective	People with insecure attachment styles are more at risk for depression in adulthood.
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Table 1: Common causes of depression

1.4 Types of Depression

Depressive disorder is characterized by periods in which a person becomes very sad, among other symptoms. The basic element of this disorder is called dysphoria. There are several types of depression, including major depressive disorder (including major depressive episode), persistent depressive disorders (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, DMDD or disruptive mood dysregulation disorder, depressive disorder due to another medical condition, and other specified and unspecified depressive disorders. ⁵

1.4.1 Major Depressive Disorder

Major Depressive Disorder, or MDD, includes periods of acute depressive symptoms called periods of major depression. The criteria for diagnosing major depression includes duration:

At least one of the following two:

- (1) Depressed mood or
- (2) Loss of interest or pleasure

Along with 5 or more of the following symptoms for at least two weeks:

- 1) Depressed mood for most of the day almost every day (such as the feeling of emptiness or sadness that can be associated with irritable mood in children and adolescents).
- 2) Significant decrease in interest or enjoyment in all or most daily activities most of the day

- 3) Significant weight loss or gain or loss or increase in appetite almost every day (failure to gain weight can be observed in children)
- 4) Insomnia or hypersomnia nearly every day
- 5) Psychological-mental agitation or slowness observed by others nearly every day
- 6) Fatigue or lack of energy nearly every day
- 7) Feeling worthless or feeling too guilty or inappropriate nearly every day
- 8) Difficulty keeping focus or decision making nearly every day
- 9) Frequent thoughts of death without a specific plan or having suicidal thoughts, plans or actions

It should be noted that these symptoms cause significant clinical disturbances in various fields and functions, such as the job position and the person's social status and performance. These symptoms are not due to the direct physiological effects of a substance or a clinical disease (such as hypothyroidism), and there is never a manic or hypomanic episode in the symptoms of major depression unless it is related to drug use or another medical condition. It should also be noted that people's response to bereavement or a serious problem such as severe financial losses can also cause symptoms similar to a depressive episode such as insomnia and loss of appetite and weight⁵. But it should be noted that MDD should be distinguished from normal sadness or bereavement, although in patients who are bereaved, MDD can be diagnosed if the depressive symptoms are severe and persistent, which also requires careful clinical examination and It has a history of the patient and his mental condition.⁵

1.4.2 Persistent Depressive Disorder (Dysthymia)

Mood swings that occur with major depressive disorder can take a chronic, persistent form. People with the disease have a more limited set of symptoms than children with major depressive disorder for at least 2 years and for children and adolescents for 1 year; these include sleep and appetite disorders, difficulty concentrating and making decisions, low self-esteem, low energy or fatigue, and feelings of hopelessness.⁴

1.4.3 Disruptive Mood Dysregulation Disorder

When children show severe and chronic irritability and have frequent outbursts of anger that occur, on average, three times a week or more, for at least 1 year, and in at least two situations, mood disorders morality is recognized for this group of children. Diagnostic criteria state that the diagnosis should not be made for children whose first period occurs when they are younger than 6 years or older than 18 years. However, clinicians should determine by direct observation of the child or his or her history that the disorder started before the age of 10. The authors of DSM-5 also believe that it is important to diagnose the disorder in children and adolescents who have previously been diagnosed with bipolar disorder. Follow-up data from children who exhibit this pattern of severe irritability and outbursts of anger also indicate that they are at risk for depressive or anxiety disorders when they reach adulthood, rather than developing bipolar disorder.⁴

1.4.4 Premenstrual Dysphoric Disorder (PMDD)

Women who experience depressed mood or changes in mood, boredom, irritability, and anxiety during the premenstrual period, which subside after the start of the menstrual cycle in most of last year's cycles, are diagnosed with PMDD.⁴ In fact, in women with PMDD, mood symptoms occur only in the luteal phase of the menstrual cycle (ovulation to the onset of menstruation) and disappear after the onset of menstruation. The diagnosis of PMDD is usually made when the patient has at least 5 of the following 11 symptoms:

- 1) Depressed mood
- 2) Marked affective lability
- 3) Persistent or marked anger or irritability
- 4) Anxiety
- 5) Appetite disturbances,
- 6) Decreased interest
- 7) Sleep disturbances
- 8) Concentration problems
- 9) Feeling overwhelmed or out of control
- 10) Physical symptoms such as breast tenderness, bloating, headache
- 11) Decreased energy or lethargy

These symptoms must be so severe that they significantly interfere with a person's social, sexual, occupational, or academic functioning. ⁵

1.4.5 Substance/medication-induced depressive disorder

This diagnosis can be made when symptoms of depression appear within 1 month after taking a substance or medicine (narcotics or medicines such as corticosteroids, oral contraceptives) and corroborating evidence from the patient's history, examination of the patient's laboratory data from drug use, abuse, intoxication or withdrawal before the onset of depressive symptoms, in which case substance-induced depressive disorder is diagnosed. Usually, after the substances are withdrawn, depending on the half-life of the substance/drug and the presence of withdrawal symptoms, depression symptoms subside within a few days to a few weeks, and therefore this disorder is distinguished from MDD. ⁵

1.4.6 Depressive disorder due to another medical condition

Having a general medical condition can also cause psychiatric symptoms (such as hypothyroidism). ⁵

1.4.7 Other specified and unspecified depressive disorders

Depressive states that usually last ≥ 2 weeks but ≤ 2 years, and include 2 to 4 related symptoms are recorded as specified and unspecified depressive disorders in DSM-5. ⁵

Chapter 2

Drug therapy is one of the most effective methods in treating depression. Synthetic and herbal drugs can both be effective, but the first line of treatment for depression from the point of view of psychiatrists is synthetic drugs, although it seems that the side effects of synthetic drugs (such as sleep disorders, sexual dysfunction, gastrointestinal (GI) complications (such as nausea, diarrhea and vomiting), change in weight, weakness, fatigue, dry mouth, tachycardia, blurred vision, postural hypotension) are more than with herbal medicines. Therefore, herbal medicines may sometimes be alternative candidates in the treatment of depression. In this chapter, 14 anti-depressant herbal medicines introduced by Iranian pharmaceutical companies and pharmacies and the plants used in them have been investigated.

2.1 Anti-Depressant Herbal Medicines

Hypiran, Perforan, Nervoxin, Rose oral drop, Rocina, SaffroMood, Cephalum Urtica, Deproherb drop and capsule, Epion, Simosleep tablet, Lavender syrupe, Ginkogol, Ginkgo TD tablets and GinSin capsule.

2.2 Hypiran, Perforan and Nervoxin

These herbal anti-depressants contain *Hypericum perforatum*.

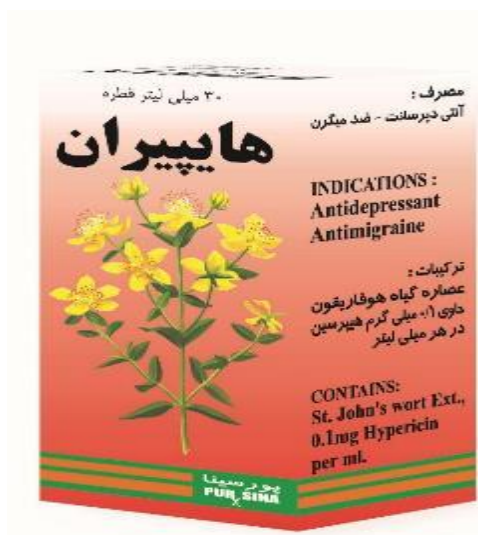


Figure 2: [Hypiran. \(July 17th, 2017\), Pursina company](#)



Figure 1: [Nervoxin, Dineh company](#)



Figure 3: [Perforan. \(January 22, 2020\), Goldaru company](#)

Medicine name	Perforan
Name of manufacturer	Goldaru company
Dosage of drugs and active ingredients	Contains 160 mg of dry extract of <i>Hypericum perforatum</i> in each tablet Standardized in terms of 300 micrograms of hypericin per tablet
Indications	Anti-anxiety Anti-depressant Anti-nervous restlessness
Consumption instruction	Three times a day, one to two tablets with a glass of water in adults
Side effects	Rarely gastrointestinal side effects such as feeling full or constipated Rarely allergy complications and photodermatitis

	Also not recommended during pregnancy and lactation
Drug interactions	Ant-icoagulants Anti-hypertensive drugs Drugs that have similar functions such as SSRIs, MAOIs Drugs metabolized by cytochrome P-450 such as cyclosporine, warfarin, digoxin, theophylline, oral contraceptives
Medicine name	Nervoxin
Name of manufacturer	Dineiran company
Dosage of drugs and active ingredients	Hypericum extract 400 mg per tablet
Indications	Mild to moderate depression Anxiety Mood disorders caused by the change of seasons Complications of mental disorders such as premenstrual syndrome, pediatric enuresis, etc.
Consumption instruction	Adults: 1 to 2 tablets daily with food (in some cases up to 5 tablets can be increased) Children 6 to 12 years: Under the supervision of a doctor half the adult dose
Side effects	Rarely light sensitivity
Drug interactions	Concomitant use with drugs metabolized by cytochrome P-450 Other standard anti-depressants Anticoagulants

	Digoxin Contraindicated in transplant patients and individuals with HIV-positive antibodies treated with indinavir Contraindicated in pregnancy and lactation An hour or two apart if used concomitantly with foods high in tyramine and iron supplements
Medicine name	Herbal drop Hypiran
Name of manufacturer	Pursina company
Dosage of drugs and active ingredients	30 ml
Indications	Treatment of depression and anxiety Migraine headaches and menstrual headaches
Consumption instruction	2 to 3 times a day, 20 to 30 drops in water each time and drink
Side effects	Possibility of allergic reactions and sensitivity to light
Drug interactions	Not recommended during pregnancy and lactation Anti-AIDS drugs Oral contraceptives Other standard antidepressants Drugs metabolized by cytochrome P-450

Table 2: Herbal medicines containing SJW.

2.2.1 *Hypericum perforatum*

St. John's wort (SJW), tea grass or *Hypericum perforatum* from the genus Hypericaceae is an annual herbaceous plant with opposite leaves and yellow flowers, which is one of the most well-known western plants. The compounds of this plant include naphthodianthrone (such as hypericins, pseudohypericin), flavonoids (such as quercetin and hyperoside), biflavonoids (such as biapigenin), xanthenes and phloroglucinol derivatives (such as hyperforin). Other components of this plant include volatile oils, tannins and caffeic acid derivatives.^{6, 7}



Figure 4: [Hypericum perforatum](#)

Therapeutic uses of this plant include the treatment of mild to moderate depression, anxiety, muscle aches, bruises and first-degree burns (topically), kidney and lung disorders and sleep disorders.⁶ Although the exact mechanism of this plant is not well understood, its constituents' effects on serotonin receptors greatly exaggerated and are widely reported to be responsible for the anti-depressant activity in this plant. The extract of this plant is also reported to nonselectively inhibit the reabsorption of serotonin, dopamine, norepinephrine and many other transmitters *in vitro*. Other studies have reported that the compounds in this plant, instead of inhibiting serotonin reuptake, may directly release monoamines and other neurotransmitters from synaptosomes *in vitro*. Many trials have shown the effectiveness of this plant in treating mild to moderate depression, as well as its superiority over placebo. In addition, St. John's wort has a similar effectiveness to some standard synthetic anti-depressants such as fluoxetine and imipramine but with fewer side effects. However, the drug interactions of this plant should not be ignored.^{6, 8}

In a meta-analysis, 29 studies in 5,489 patients with major depression treated with SJW for 4 to 12 weeks showed that the SJW was more effective than placebo and similar in effect to some standard anti-depressants. Among these trials, 18 trials compared SJW extract with placebo, 17 trials reviewed hypericum with standard anti-depressants, and six trials had a placebo and a control group of standard anti-depressants. The results showed the superiority of SJW over placebo. Also, the tests showed that SJW is as effective as other standard anti-depressants, and at the same time, it has fewer side effects.⁹

In another trial that compared SJW with the synthetic drug imipramine, 324 participants with mild to moderate depression were given either 75 mg of imipramine (twice a day) or 250 mg of SJW extract (twice a day) was given to patients for 6 weeks. At the end of the experiment, it was found that SJW has the same effectiveness as imipramine and is better tolerated than imipramine.⁸

Primary variable	Treatment		Difference of least square means (95% CI)*	P value†
	Hypericum (n=157)	Imipramine (n=167)		
Hamilton depression rating scale‡				
Change from baseline score	12.00	12.75	-0.75 (-1.90 to 0.40)	0.20
Change from baseline score (analysis of data from patients who complied with protocol)	11.53	11.21	0.32 (-0.72 to 1.36)	0.55
Secondary variables				
Hamilton depression scale:				
Score on anxiety-somatisation subscale	3.79	4.26	-0.48 (-0.91 to -0.04)	0.03
Score on depression subscale	4.33	4.57	-0.24 (-0.74 to 0.26)	0.35
Score on clinical global impression scale‡	2.22	2.42	-0.20 (-0.42 to 0.02)	0.08
Score on patient's global impression scale‡	2.44	2.60	-0.16 (-0.40 to 0.09)	0.20
Score of patient's assessment of tolerability	1.67	2.35	-0.68 (-0.88 to -0.49)	0.00

*Least square means are derived from the general linear model (analysis of covariance). The means are adjusted (end points reflect changes corrected for baseline values).

†P values are exploratory; they are derived from the statistical analyses conducted to construct confidence intervals.

‡Lower scores indicate greater improvement.

Table 3: The effect of treatment with imipramine and SJW in 6 weeks. ⁸

Although SJW has performed better than placebo in most trials and has been almost as effective as some synthetic anti-depressants, it is important to consider the drug interactions of this plant with certain other drugs.

Skin complaints, dizziness, headache, fatigue, insomnia, confusion, dry mouth, irritability and anxiety are common (though mild) side effects of this plant. Sensitivity to light also rarely occurs with high doses of this drug. The cause of this complication can be related to the quinone compounds (primarily hypericin) in this plant, which when exposed to light, produce singlet oxygen and free radicals. In addition, some studies have shown that hypericin is excreted in small

amounts in breast milk of mothers who took 300 mg of SJW 3 times a day, but did not cause side effects in the mother or baby, however, more studies are needed in this area. ⁶

Studies have shown that chronic administration of SJW can reduce plasma levels of some drugs by inducing the enzymes CYP 3A4 and P-glycoprotein. SJW has also been suggested to interfere with other antidepressants, such as serotonin reuptake inhibitors and MAOIs. The combination of SJW with MAOI drugs would theoretically lead to a blood pressure crisis or, in combination with serotonin reuptake inhibitors, to cause serotonin syndrome though this has not been reported to occur. ⁶

2.3 Rocina and SaffroMood

These herbal anti-depressants contain saffron.

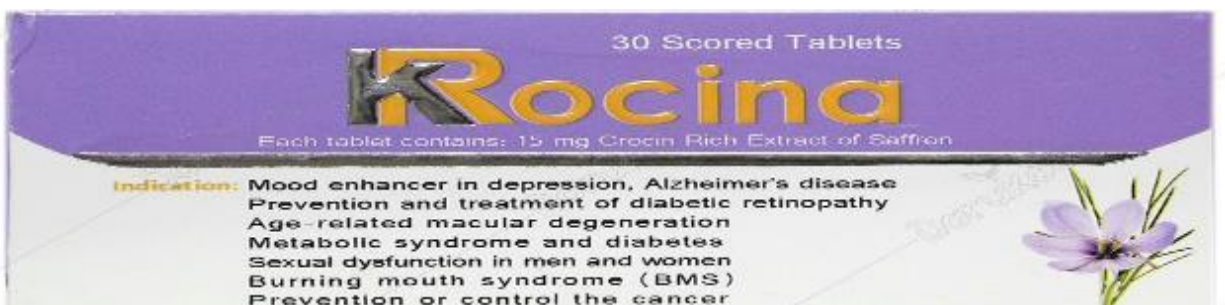


Figure 5: [Rocina, Samisaz company](#)



Figure 6: [SaffroMood, Naturalhealth](#)

Medicine name	Krocina
Name of manufacturer	Samisaz company
Dosage of drugs and active ingredients	15 mg of crocin extract per tablet
Indications	Anti-depressant Anti-anxiety Relaxing
Consumption instruction	1 to 2 times a day with food in the morning and evening
Side effects	No side effects were reported Contraindicated during pregnancy and children under 12 years
Drug Interactions	Increases the anticoagulant effect of warfarin
Medicine name	SaffroMood
Name of manufacturer	Green plants of life company
Dosage of drugs and active ingredients	15 mg of the unique composition of Saffron bio-components and a high concentration of Vitamin B6.
Indications	Anti-depressant
Consumption instruction	One capsule before breakfast and one capsule before dinner Or as directed by your doctor
Side effects	Not to be taken during pregnancy or breastfeeding

	Not to be used in children under the age of 12
Drug interactions	-

Table 4: Herbal medicines containing saffron.

2.3.1 Saffron

Saffron is a perennial plant that is used as a medicine and as a spice. This plant has various biological compounds such as safranal, crocin and picrocrocin, which are responsible for the bitter aroma and taste of saffron. Saffron stigma also contains carbohydrates, vitamins B1, B2, pigments, minerals and mucilage. The active ingredients of saffron have effects such as anti-depressant, anti-convulsant, anti-inflammatory, anti-tumor, learning and memory enhancement effects and radical scavenger. Saffron has also been used for a long time to relieve stomachaches, kidney stone pain and depression.¹⁰ Although the exact mechanism of this plant is not well understood, it seems that crocin and safranal, which are the two main components of saffron, can inhibit the reabsorption of dopamine, norepinephrine and serotonin.¹¹



Figure 7: [Saffron](#)

In a clinical trial, the clinical effect of saffron with fluoxetine in the treatment of mild to moderate postpartum depression for 6 weeks for women aged 18 to 48 years (Hamilton depression rating scale ≤ 18 , the Hamilton Rating Scale (HDRS) consists of 21 items that measure the severity of behavioral, physical, and mental symptoms of depression, including mood, guilt, suicidal thoughts, irritability, weight disorders, insomnia, and anxiety), was compared. In this

trial, participants (64 people) randomly received a 15 mg saffron capsule or a 20 mg fluoxetine capsule twice a day. At the end of 6 weeks, 6 patients in the saffron group and 7 patients in the fluoxetine group reached a HDRS $\leq$ 7. Therefore, the results of this study suggest the effectiveness of saffron in the treatment of postpartum depression and therefore saffron can be a safe alternative to fluoxetine in the treatment of mild to moderate depression.¹¹

In another trial, the effects of saffron on depression in patients undergoing coronary artery bypass grafting (CABG) were investigated. Enduring depressive symptoms along with complications after surgery can provide very difficult conditions for patients, so the use of a low-risk and effective drug in this area for these patients is very helpful. For this reason, in a clinical trial, eligible participants were selected from among those undergoing CABG surgery, and received saffron capsules or placebo in doses of 15 mg, twice a day for two days before CABG surgery for 12 weeks. At the end of the trial, no efficacy results were observed in both groups and no anti-depressant and anti-anxiety effects were observed. It should be noted, however, that patients used anesthetics, benzodiazepines, and other analgesics during treatment to reduce postoperative side effects, which may have obscured the pure effects of saffron. Also, the number of samples in this study was not large enough because most patients could not participate in the study due to side effects from surgery.¹²

In a meta-analysis that includes 7 clinical trials, the effectiveness of saffron for the treatment of mild to moderate MDD in adults has been investigated. In 3 trials of this meta-analysis, saffron was compared with placebo and in 4 other trials, saffron was compared with synthetic anti-depressants. In 6 trials, saffron was prescribed at a dose of 30 mg and only in one trial at a dose of 100 mg. The duration of treatment in these trials varied from 6 to 12 weeks. In all trials in which saffron was compared with placebo, saffron was more effective than placebo, and in the remaining four trials, saffron with TCAs or SSRIs had similar anti-depressant effects. Also, no serious side effects were observed in these trials except in a few cases (change in appetite, anxiety and nausea). In one study, in this meta-analysis, saffron petals were used instead of saffron stigmas, and the results showed the superiority of saffron petals compared to placebo. Since saffron petals are much cheaper than stigmas, using saffron as an effective and surprisingly inexpensive medicinal plant could be useful medically.¹³

2.4 Rose oral drop

This herbal antid-epressant contains the Rosa damascena.



Figure 8: [Rose oral drop, Barij essence](#)

Medicine name	Rose oral drop
Name of manufacturer	Barij Essence company
Dosage of drugs and active ingredients	15 ml, Contains R. damascena, citronellol, nerol, linalool, phenyl ethyl alcohol.
Indications	Anti-depressant and anti-anxiety Increased sexual desire in men and women
Consumption instruction	Take 15 drops twice a day with enough water each time.
Side effects	Contraindicated during pregnancy and childhood.
Drug Interactions	-

Table 5: Herbal medicine containing Rosa damascena.

2.4.1 Rosa damascena mill L.

Rose damascena is an ornamental plant that has several medicinal properties. The extract of this plant contains 300 different compounds, of which 50 are known. This plant grows well in Iran, especially in Kashan, and is used to prepare rosewater. Traditional uses of this plant include treating menstrual bleeding, digestive problems, reducing inflammation, strengthening the heart and chest and abdominal pain. Other medicinal properties of this plant include anti-HIV, anti-bacterial, anti-cough, anti-diabetic properties, as a mild laxative, anti-oxidant, treatment of depression, grief and nervous stress.¹⁵

Rose has a wide variety of chemical compounds including flavonoids, glycosides, geraniol, citronellol, terpenes, citric acid, malic acid, pectin, carotenoids and some vitamins. It is assumed that most of the medicinal effects and functions of R-damascena are related to the phenolic compounds of this plant. The mechanism of the rose flower is also thought to be through dopaminergic, adrenergic, and serotonergic mechanisms, stimulation of beta-adrenergic receptors, inhibition of H1 receptors, and blocking calcium channel of tracheal chain.¹⁶



Figure 9: *Rosa damascena* ¹⁷

In a clinical trial to investigate the effect of rose on the severity of depression in postmenopausal women, 110 postmenopausal women in Tehran in 2020 participated and received a 500 mg capsule of rose and the control group took a placebo capsule 3 times a day. The trial lasted 40 days and the average depression score was measured at the beginning and after the twentieth and fortieth days. Changes in depression score on the twentieth day of treatment were not significantly different ($P < 0.05$), but after 40 days, a significant difference was observed ($P < 0.001$). Therefore, instead of hormone therapy, the use of synthetic drugs and their side effects to treat depression in postmenopausal women, this plant was considered to be a safe treatment in this study. ¹⁶

In an animal study, the effect of rose was compared with that of amphetamine in mice. In this study, rose drops were prepared in concentrations of 5, 10, 20 and 40% and injected subcutaneously into mice. Amphetamine was also injected intraperitoneally at doses of 0.5, 1 and 2 mg/kg body weight to another group of mice. The mice were then subjected to a forced swimming test (FST) and their reduction in immobility was measured. The results showed that doses of 1 and 2 mg/kg amphetamine reduced the immobilization time of mice in FST, but the dose of 0.5 mg was ineffective. Rose drops at concentrations of 10, 20 and 40% also reduced the immobility time of mice and the maximum effect was observed at a concentration of 40%, but the dose of 5% was ineffective. ¹⁴

Therefore, this evidence suggests the possible anti-depressant effect of rose drop. However, it is important to consider that the effect of the drug in animal models is not necessarily the same as the effect in the human depression model and requires specific clinical trials in depression.

2.5 Cephalum Urtica

Cephalum urtica is an herbal anti-depressant that contains *Urtica dioica* (nettle) and *Melisa officinalis* (lemongrass).



Figure 10: [Cephalum Urtica, Mers company](#)

Medicine name	Cephalum Urtica
Name of manufacturer	MersPharma company
Dosage of drugs and active ingredients	500 ml, Contains <i>Urtica dioica</i> and lemongrass
Consumption instruction	Take 2 tablespoons 3 times a day, half an hour after each meal
Indications	Calms the nerves Anti-depressants and treatment of depression Relieve bloating caused by stress and anxiety Elimination of nerve spasms
Side effects	-
Drug Interactions	-

Table 6: Herbal medicine containing Cephalum Urtica

2.5.1 *Urtica dioica*

Urtica dioica (nettle) is a medicinal plant that has long been used to treat stomachaches, rheumatic pains, colds and coughs. This plant has many anti-oxidant properties and contains the glycosides kaempferol and caffeic acid ¹⁸.



Figure 11: *Urtica dioica* ¹⁸

Due to the high anti-oxidant properties of this plant and its other healing properties, a trial has been conducted to investigate the anti-depressant effects of this plant. In this study, an animal model (78 mice) was used and the groups included the control group, the positive groups receiving fluoxetine (10 mg/kg) and haloperidol (1 mg/kg), the groups receiving urtica (50, 100 mg/kg) extract and *Elastostema umbellatum* (50, 100 mg/kg). The drugs were then injected intraperitoneally into mice on the first and third days 30 minutes before the FST or TST (tail suspension test). Then, the total immobility time was recorded in the last 6 minutes of these 10-minute tests. ¹⁹

Name of extract	Dose (mg/kg)	Forced swimming test				Tail suspension test	
		Immobility time ^a (s) at first day	Change (%)	Immobility time ^a (s) at third day	Change (%)	Immobility time ^a (s)	Change (%)
Control	0	379.00±31.50	-	387.00±52.80	-	326.30±30.40	-
Haloperidol	1	106.70±4.50***	-71.84	75.00±8.20***	-80.62	64.00±15.10***	-80.39
Fluoxetine	10	203.70±6.10***	-46.25	201.00±7.00***	-48.06	98.00±11.50***	-69.97
CEUD I	50	225.33±25.01***	-40.55	134.67±6.11***	-65.20	139.33±8.51***	-57.30
	100	168.67±35.57***	-55.50	133.33±30.92***	-65.55	105.00±13.08***	-67.82
BEUD II	50	296.67±3.51***	-21.72	178.33±8.08***	-53.92	140.00±6.00***	-57.09
	100	266.67±4.51***	-29.64	176.00±31.75***	-54.52	127.33±2.52***	-60.98
BEUD II ₂	50	276.00±12.29***	-27.18	122.67±8.02***	-68.30	135.00±5.37***	-58.63
	100	193.00±19.97***	-49.08	105.00±9.64***	-72.87	111.00±3.64***	-65.98
HEEU I	50	292.00±13.08***	-22.96	196.67±32.00***	-49.18	287.67±15.28 ^{ns}	-11.84
	100	260.67±12.50***	-31.22	180.33±17.50***	-53.40	252.33±27.50***	-22.67
MEEU II	50	268.67±41.63***	-29.11	110.33±12.22***	-71.49	308.33±33.98 ^{ns}	-5.51
	100	206.33±7.37***	-45.56	100.33±10.2***	-74.07	275.00±18.68 ^{ns}	-15.72

^aMean±SD, n=6; Statistically significant difference compared to the control group of animals: *** P=0.05, ** P<0.010, * P<0.001 and ns=Data are not different significant compared to control (vehicle). CEUD I: chloroform extract of *U. dioica* from extraction method I; BEUD II: butanol extract of *U. dioica* from extraction method II; BEUD II₂: fraction number 2 from the butanol extract of *U. dioica* from extraction method II; HEEU I: hexane extract of *E. umbellatum* from extraction method I and MEEU II: methanol extract of *E. umbellatum* from extraction method II

Table 7: Anti-depressant effect of selected crude extracts of *E. umbellatum* and *U. dioica*.¹⁹

The results showed that the anti-depressant-like effects of these plant extracts were comparable to haloperidol and fluoxetine and the acute administration of these extracts was similar to fluoxetine and haloperidol. Despite the suggestion of the possible anti-depressant properties of nettle in this study, human clinical trials are needed to investigate the anti-depressant effect of *Urtica dioica*.

2.5.2 *Melisa officinalis* or Lemon Balm

Melisa officinalis (lemon balm) is a medicinal plant containing flavonoids, phenolic acid, tannins and volatile oils. Traditional uses of this plant include the treatment of depression and vitality, sleep disorders and reduction of nervous system disorders (reduction of irritability and anxiety). New findings also show the anti-bacterial and behavioral modulating properties of lemon balm.²⁰



Figure 12: [Melisa officinalis](#)

In a clinical trial involving a total of 45 adult patients with mild to moderate depression, the anti-depressant effects of lemon balm and lavender were compared with fluoxetine. The experiment was performed on patients for 8 weeks and patients were divided into 3 groups of lemon balm, fluoxetine and lavender and drugs were prepared in a dose of 500 mg (fluoxetine containing 5 mg of fluoxetine and 495 mg of starch powder). Finally, in the eighth week, a significant decrease in Hamilton depression score was observed in all three groups, and lemon balm and lavender had equal effect as fluoxetine with lower side effects and drug dependency in comparison to fluoxetine.²⁰

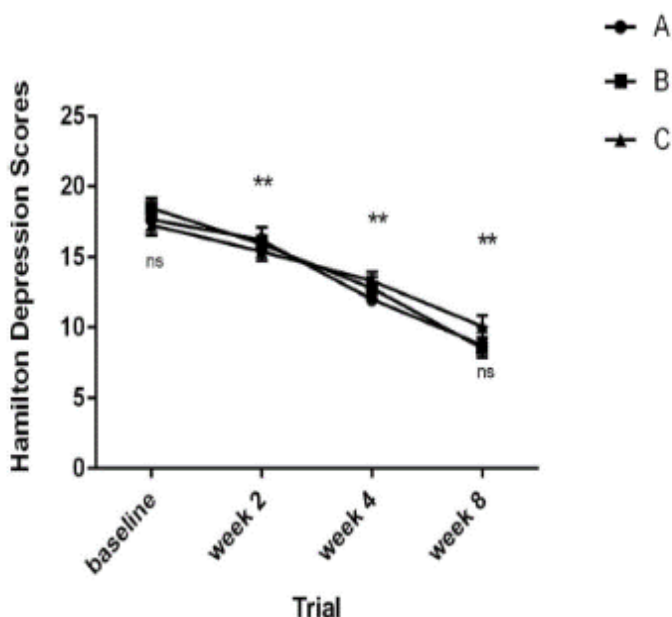


Figure 13: Graphs of Hamilton depression scores in three groups of Fluoxetine, Lavender and Melisa officinalis. This figure is taken from reference.²⁰

Mean + – S.E.M. scores of *Lavandula angustifolia* (Group A), Fluoxetine (Group B) and *Melissa officinalis* (Group C) on the Hamilton Depression Rating Scale. The horizontal symbol (**) was used to express statistical significance versus their respective baseline value and the symbol ns (no significance) were used for between-group comparisons.

2.6 Deproherb drop and capsule

Deproherb is an herbal anti-depressant that contains *Pelargonium graveolens* var. *roseum* (rose geranium).



Figure 14: [Capsule Deproherb, Barij essence](#)

Medicine name	Deproherb soft capsule
Name of manufacturer	Barijessence
Dosage of drugs and active ingredients	50 mg soft capsule - contains pelargonium roseum- Standardized based on the presence of 15-22 mg of citronellol in each soft capsule.
Consumption instruction	Twice a day, each time take a soft capsule after a meal with some fluids.
Indications	Anti-depressant
Side effects	No specific side effects have been reported, but it may increase the effectiveness of other anti-depressants.
Drug Interactions	Due to the lack of sufficient evidence, the use of this product in children, during pregnancy and lactation is not allowed.

Table 8: Medicine containing Lemon Balm

2.6.1 *Pelargonium graveolens* (rose geranium)



Figure 15: *Pelargonium graveolens*

Pelargonium roseum is a medicinal plant that has different compounds such as geraniol, citronellol, menthone, citronellyl formate and geraniol acetate, which has a wide range of different activities due to having these compounds²². The anti-depressant activity of this plant has been suggested in clinical trials. In one of these trials, 118 postmenopausal women with a score of 14 or higher were divided into three groups: control, massage, and aromatherapy massage, and were treated with vegetable oils for 30 minutes once a week for 8 weeks (*Pelargonium roseum* and almond oil) were included. The aromatherapy massage group received 2% of geranium oil in almond oil, which means that in addition to the massage with sweet almond oil, they also inhaled the aroma of geranium, but the massage group received massage only with almond oil. In this study, massage was performed by the effleurage method and massage oil was applied on the abdomen, back and arms without pressure and with the palms of the hands or fingers. After 8 sessions of treatment, the depression scores of the massage recipients decreased compared to the control group, but this decrease was greater in the aromatherapy massage group than in the massage group alone.²¹

	Before ^a	After ^a	Mean Difference 95%CI	P-Value
Aromatherapy massage	1.01 ± 0.19	0.5 ± 0.17	0.51	0.001
Massage therapy	1.01 ± 0.22	0.81 ± 0.15	0.20	0.001
Control	1.00 ± 0.16	1.00 ± 0.15	0.00	-

Table 9: Measuring Effects of Aromatherapy Massage and Massage Therapy on Depression.²¹

Therefore, aromatherapy massage with aromatic geranium oil can reduce menopausal depression. Various studies have shown that stimulation of the brain by odors can improve blood flow to the frontal cortex, and since some cases of depression may be associated with decreased

brain metabolism and blood flow to the frontal lobe, aromatherapy along with the beneficial effects of massage can have positive results in the treatment of depression and reduce depressive symptoms. In this study, no side effects were reported by the participants and aromatherapy massage was able to show its suggested role in treating depression in postmenopausal women with mild to moderate depression. However, more studies and longer-term trials are needed to provide definitive results.²¹

Another experiment using 200 mg/kg of inhaled geranium was shown to have an effect on the depressive-like behavior of mice. In this study, animals were divided into three groups of control (dist. Water 10 mg/kg, p.o), imipramine (15 mg/kg, p.o) and geranium oil (200 mg/kg, inhalation method) and were treated for 14 days. In this trial, tests such as FST, TST and OFT or open field test were used. In all of these tests, the inhaler was placed on the floor of the room and consisted of a cotton ball soaked in geranium oil that the animal was exposed to perfume for 7 minutes. In the TST test, the animals were hung from a tail on a metal rod at a height of 50 cm above the ground with the help of adhesive tape, and at first, they tried to escape by making strong movements, but when they were completely fixed, they were considered immobile. In the FST test, the animals had to swim in a plastic cylinder containing water at a depth of 20 cm, and in this cylinder, the rats could not make contact with the walls or the bottom of the container, and when they completely stopped fighting, they remained motionless. In the open field test, the mice were placed separately in a wooden box with the floor divided into 12 squares, and their number of crossings in the squares with the four paws and time spent in their periphery squares and time spent in center squares were recorded. The results showed that geranium oil and imipramine reduced the duration of immobility and time spent in the periphery compared to the control group and also increased the time spent in the center. Therefore, this study shows that geranium oil has anti-depressant-like behavioral properties in animals, but human clinical studies are needed to show an actual anti-depressant effect for this plant.²²

2.7 Epion



Epion is another herbal anti-depressant available in the Iranian market that contains herbs such as *Hypericum perforatum*, passionflower and valerian.

Figure 16: [Epion, Irandarouk](#)

Medicine name	Epion
Name of manufacturer	Irandarouk

Dosage of drugs and active ingredients	Tablet weight 350 mg Each tablet contains 65 mg of <i>Hypericum perforatum</i> extract, 70 mg of Passiflora dried extract and 30 mg of valerian dry extract.
Consumption instruction	Children 6 to 12 years: 1 to 3 tablets a day in consultation with a physician Adults: 1 to 2 tablets three times a day, maximum 5 tablets per day (in case of insomnia, take 1 to 2 tablets one to two hours before bedtime)
Indications	Sedatives, anti-depressants and anxieties, relieving nerve spasms and relieving sleep disorders of neurological origin
Side effects	Very few stomach problems, allergic reactions and early drowsiness
Drug interactions	Concomitant use of heparin, warfarin, digoxin, benzodiazepines and barbiturates, drugs metabolized by cytochrome P450 (such as birth control pills, cyclosporine, etc.), serotonergic drugs (such as nefazodone), theophylline, simvastatine, and verapamil. Concomitant use with drugs with similar mechanism (MAO enzyme inhibitors), concomitant use with immunosuppressive drugs (cyclosporine, tacrolimus, etc.), non-nucleotide inhibitors used in the treatment of HIV, cytostatic drugs except monoclonal antibodies. Concomitant use of alcohol, consumption in children under 6 years, in pregnancy and lactation, people with skin allergies to sunlight is not recommended.

Table 10: Epion, containing Valerian, Passiflora and *Hypericum perforatum*

2.7.1 *Valeriana officinalis*

(Valerian)



Valerian is a perennial plant native to North America, Asia, and Europe that contains compounds such as volatile oils, ketones, phenols, alkaloids, and iridoidesters such as valeric acid, valproate, and amino acids such as aminobutyric acid, tyrosine, and some hydrocarbons. This plant has been prescribed for many years as a sedative and hypnotic plant, but it also may have anti-depressant effects. It has been suggested that the anti-depressant and mood stabilizing effects are due to the plant's ability to interfere with noradrenergic and dopaminergic neurotransmitters, as well as GABA and serotonin.²³

Figure 17: [Valerian](#)

The anti-depressant, anti-anxiety and sleep quality of this plant have been studied in various trials. In one of these randomized, double-blind, placebo-controlled trials in Semnan hospitals, participants (39 people) were selected from hemodialysis patients suffering from depression, anxiety, and sleep disorders. Depression and sleep disorders are very common in hemodialysis patients and most of them suffer from sleep disorders which can be an important risk factor for depression in these patients. This trial consisted of two stages. In the first stage, participants were divided into 2 groups: group A (recipients of valerian capsules containing 530 mg of dried valerian root) and group B or control (recipients of placebo capsules containing 50 mg of starch) and were treated for 1 month. Then, in the second phase of the diet, the two groups changed and group A received placebo and the other group received valerian. The results showed that in the first stage in group A the decrease in depression score was more than group B and in the second stage it was the opposite.²³

Therefore, valerian can be a safe treatment for depression in hemodialysis patients by treating sleep disorders followed by lowering depression scores. However, generalizing the results of this trial is not possible, since specifically designed trials are needed to confirm the anti-depressant effects of this plant.²³

2.7.2 *Passiflora incarnata* (Passion-flower)



Figure 18: [Passion flower](#)

Passiflora incarnata is a plant native to Brazil, which is cultivated in many parts of the world, including northern Iran. Because this plant looks like a clock, it is called a passionflower. The flowers of this plant are blue and its fruits are green, which turn orange when ripe. Compounds such as flavonoids, cyanogenic glycosides, indole alkaloids and other alkaloids such as harmaline, harmine and harmalol are present in its structure. The properties of passionflower include analgesic, sedative, hypnotic, antispasmodic, treatment of mild to moderate depression, general epilepsy, premenopausal syndrome, viral infections, seasonal mental disorders and restlessness.

24, 25

An uncontrolled clinical trial using extracts of either passionflower or *Hypericum perforatum*, was associated with an improvement in the depression in postmenopausal women. In this trial, 59 postmenopausal women who had the necessary conditions to enter the study were divided into two treatment groups and their symptoms were assessed before the study, in the third and sixth weeks, and participants completed the Cooperman questionnaire. *Hypericum perforatum* in the form of effervescent tablets 160 mg 3 times a day and Passionflower 30 mg 10 drops, 3 times a day and 30 drops to be taken before bedtime. The results suggest that both plants may have resulted in a significant reduction in menopausal symptoms, including depression. Symptoms such as anger, palpitations, tingling sensation, depressed mood, and muscleaches

improved significantly in the first three weeks, and these symptoms appeared to have responded to treatment very quickly.²⁴

The anti-depressant-like activity of the hydroalcoholic extract of passionflower has been studied in another trial in male mice in TST and FST tests. In this study, 48 male mice were randomly divided into 6 groups: negative control group, positive control groups (fluoxetine 20 mg/kg and imipramine 30 mg/kg), passionflower extract treatment groups (200, 400 and 800 mg/kg). All drugs and extracts were dissolved in 0.9% normal saline and administered intraperitoneally at a constant volume of 10mg/kg, and mice were placed separately in tests 30 minutes after injection. The results shows that passionflower, fluoxetine and imipramine extracts reduced immobility time compared to the negative control group. This study shows that passionflower has significant effects in animal models of depression, but further studies are needed to determine any possible mechanisms for passionflower.²⁵

2.8 Lavender

Lavender can be used both orally and topically and inhaled. To benefit from the properties of this medicinal plant locally, you can put a few drops of it on the desired area and also inhale its smell.



Figure 19: [Lavender syrup, Exir company](#)

Medicine name	Lavender syrup
Name of manufacturer	Herbalexir company

Dosage of drugs and active ingredients	120 cc Contains lavender
Consumption instruction	15 ml per night (3 tablespoons of jam)
Indications	Depression treatment Treatment of anxiety and insomnia Tonic for the brain Cleansing phlegm from the brain
Side effects	-
Drug Interactions	Concomitant use of anticoagulants increases the risk of bleeding In combination with sedatives it may increase depression It is contraindicated in case of allergies and also during pregnancy

Table 11: Medicine containing lavender

2.8.1 Lavender



Figure 20: [Lavender](#)

Lavender is an aromatic and evergreen plant that grows natively in the Mediterranean sea. The main constituents of this plant are linalool, linalyl acetate, tannins and other compounds. Linalool in this plant affects the levels of noradrenaline and dopamine, can improve blood flow to the brain and also its effects on gamma aminobutyric acid (GABA) have been reported. ²⁶

In a clinical trial, the topical effect of lavender on depression was studied. In this study, 141 women at 25 to 28 weeks of gestation were randomly divided into 3 groups: lavender cream, lavender cream with foot bath, and placebo group, and were treated for 2 months, but after 8 weeks, they stopped the treatment so as not to disturb the delivery. Also to prevent possibility of the loss of blinding due to the different smell of lavender and placebo cream, It was explained to the participants that only the effect of a herbal cream would be investigated without mentioning lavender. Participants applied topical lavender cream on their legs before going to bed, and in the foot bath method, 30 minutes after applying the cream, they soaked their feet in water at a temperature of 40 to 42 degrees for a depth of 5 cm for 10 to 20 minutes. In the fourth week of treatment, the depression scores in the groups were not significantly different from each other, but in the eighth week, the depression scores in both groups were significantly lower than placebo. Therefore, the results suggest that 8 weeks of using lavender cream is necessary to reduce symptoms of depression. Since the depression scores in the two treatment groups were not significantly different from each other, it seems that foot bath did not improve effectiveness over the cream alone. Although lavender is not recommended during the first trimester of pregnancy, it is safe in the second and third trimesters and can improve the quality of life of pregnant women with mild to moderate depression.²⁷

In another study, the potential anti-depressant effect of lavender was investigated on 60-year-olds. In this study, 60-year-olds were divided into two control groups (the control group did not receive any placebo) and the intervention group (30 people in each group), and for two weeks, they were given two grams of lavender tea bags in a boiled form, twice a day, morning and night. The average score of depression before and after drinking lavender was 17.80 ± 1.49 and 16.33 ± 1.49 , respectively. Although this effect is very small, it can be used as a complementary treatment in reducing depression due to its cheapness and availability.²⁶

2.9 Ginkgol and Ginkgo TD tablets



Figure 21: [Ginkgo TD, Mosbatesabz](#)



Figure 22 : [Ginkogol, Goldaru](#)

Medicine name	Ginkogol tablet
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Name of manufacturer	Goldaru company
Dosage of drugs and active ingredients	Each tablet contains 40 mg of standardized dry extract of <i>Ginkgo biloba</i> leaves Standardized based on 8.4-11.3 mg of ginkgo glycosidic flavonoids per tablet
Consumption instruction	1 to 2 tablets 3 times a day
Indications	Help treat disorders and symptoms of cerebral circulatory disorders such as dizziness, depression, fatigue, tinnitus, memory disorders, dementia
Side effects	It is associated with minor side effects, and spontaneous bleeding and headache have been reported rarely.
Drug Interactions	Do not take with nonsteroidal anti-inflammatory drugs and anti-coagulants and platelets. Use with caution during pregnancy and lactation
Medicine name	Ginkgo TD
Name of manufacturer	Tolid-daru company

Dosage of drugs and active ingredients	Each tablet contains 40 mg of dried <i>ginkgo biloba</i> leaf extract
Consumption instruction	Adults should take 1 to 2 tablet every 8 hours
Indications	Strengthen memory and treat depression Improves ringing and tinnitus Improve brain function Relieve dizziness
Side effects	-
Drug Interactions	It is contraindicated in people with a history of seizures and those taking anti-hypertensive drugs, as well as in people with coagulation problems or those taking drugs that prolong coagulation time.

Table 13: Medicines containing Ginkgo biloba

2.9.1 Ginkgo biloba



Figure 23: [Ginkgo biloba](#)

Ginkgo biloba tree has been used as a medicinal plant since ancient times. Ginkgo biloba extract (EGB) is prepared from the green leaves of the Ginkgo biloba tree, which contains compounds such as flavonoids such as quercetin glycosides and kaempferol glycosides. Research has shown that *Ginkgo biloba* green leaf extract has various effects on improving mood and cognitive function, protecting against central nervous system disorders and memory deficits.²⁸

A randomized clinical trial study was performed with a control group to evaluate the effectiveness of *Ginkgo biloba* as an adjunctive therapy in patients with depression. In this study, a total of 136 patients (≥ 60 years old) were selected and divided into two groups of patients treated with citalopram (20 mg orally, once daily) and patients treated with citalopram + (Egb) ginkgo biloba (19.2 mg 3 times a day). In the second week of treatment, the effective rate (defined as at least 50% reduction in Hamilton depression score) in the Cit+ Egb group was 81% and in the Cit group was 44%, and until the end of the treatment (12 weeks), the effect rate in the Cit+EGB group was more than the citalopram group.²⁹

Groups		Cure	Significant improvement	Improvement	Invalid	Effective rate
Cit group	2 weeks of treatment	7	10	13	38	44.12%
	4 weeks of treatment	14	19	20	15	77.94%
	6 weeks of treatment	21	20	17	10	85.29%
	8 weeks of treatment	30	17	14	7	89.70%
	12 weeks of treatment	40	13	11	4	94.12%
EGb + Cit group	2 weeks of treatment	15	18	22	13	80.88%*
	4 weeks of treatment	22	19	16	11	83.82%
	6 weeks of treatment	29	16	15	8	88.23%
	8 weeks of treatment	38	14	11	5	92.65%
	12 weeks of treatment	46	12	8	2	97.06%

EGb = ginkgo biloba extract.
 * Comparison with Cit group, $P < .05$.

Table 14: Comparison of clinical effects of 2 groups. This table is taken from reference. ²⁹

The results also showed that the combination of citalopram with *ginkgo biloba* did not increase side effects. Therefore, combining *ginkgo biloba* with citalopram may have a synergistic role to help reduce depressive symptoms. However, the anti-depressant effects of this plant should be investigated in trials with a larger statistical population, and long monitoring and other research are needed to elucidate the molecular mechanism of this plant. ²⁹

In another study, TST and FST tests were used on animal models to investigate the possible effect of *Ginkgo biloba* leaf extract on depression. In this study, mice were divided into two groups of 35 and 50 rats and mice. The group of 35 rats was divided into 5 subgroups (the group receiving imipramine orally at 15 mg/kg body weight, 3 groups receiving EGB at doses of 5, 10 and 50 mg/kg of body weight, the vehicle group that received deionized water) and they were treated for 14 days and FST test was done for them. ²⁸

The group of 50 mice was randomly divided into five groups (the group receiving imipramine inter-peritoneally at 30 mg/kg body weight, 3 groups receiving EGB, interperitoneally at doses of 10, 50 and 100 mg/kg of body weight, the vehicle group that received deionized water) and the test solutions were injected into the mice 30 minutes before the TST test and they were treated for 14 days. The results showed that EGB with doses of 10 and 50 in the FST test and with doses of 50 and 100 in the TST test was able to reduce the time of immobility (depression-like states in animal models) after two weeks (figures 22 and 23). ²⁸

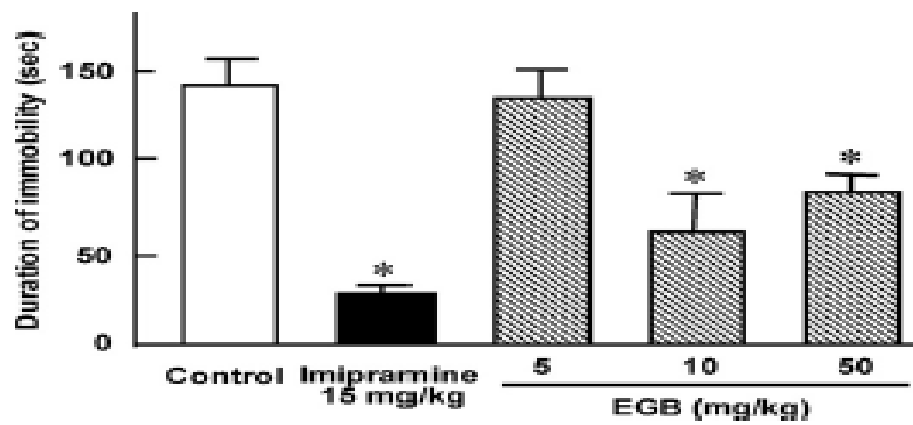


Figure 24: Effect of EGB on Immobility Time in the FST Using Rats ²⁸

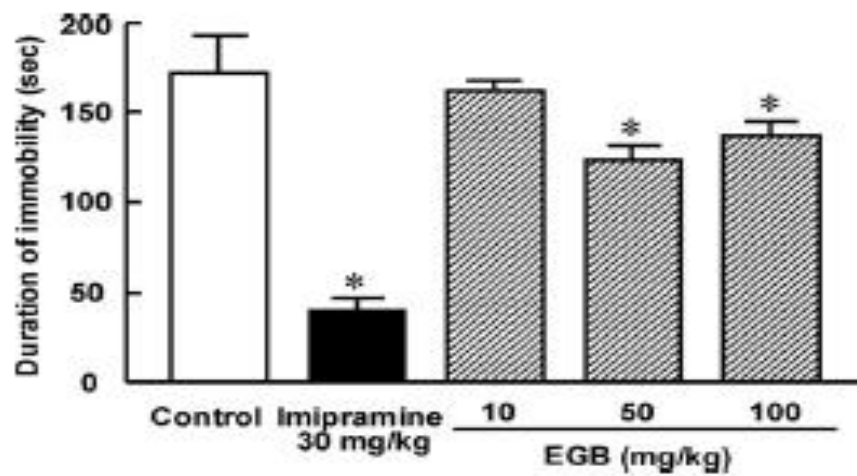


Figure 25: Effect of EGB on Immobility Time in the TST Using Mice ²⁸

2.10 Simosleep tablet

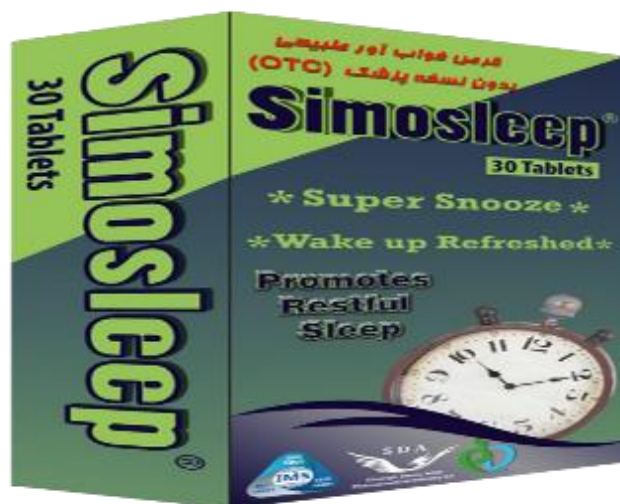


Figure 26: [Simosleep tablet, Simorghdarou company](#)

Medicine name	Simosleep Tablet
Name of manufacturer	Simorghdarou company
Dosage of drugs and active ingredients	Valerian root powder: 100 mg Chamomile flower powder: 50 mg Hops flower powder: 50 mg Passionflower aerial powder: 25 mg
Consumption instruction	1 tablet a day, half or an hour before bedtime

Indications	Help treat depression caused by melatonin deficiency Help regulate sleep on long air trips Has antioxidant and anti-cancer properties Help cure sleep
Side effects	-
Drug Interactions	Concomitant use of this drug with sedatives and hypnotics, anticoagulants, immunosuppressive drugs and blood pressure medications is not recommended. It is also not recommended for use during pregnancy, lactation and for people under 18 years of age. This medication should be stopped at least two weeks before surgery.

Table 12: Simosleep tablet, containing hops

2.10.1 *Humulus lupulus* (hops)



Figure 27: [*Humulus lupulus*](#). (27 August 2010T)

Humulus lupulus is widely used as a medicinal plant as well as a bitter agent in the beer industry. This plant also has anti-fungal, anti-bacterial and anti-spasmodic properties and has traditionally been used to improve appetite and digestion, treat irritability and restlessness associated with tension headaches, toothaches and earaches. The compounds in this plant include terpenes, bitter acids, chalcones, flavonol glycosides and catechins.³⁰ The bitter alpha acids in this plant seem to have sedative and anti-depressant effects. Hops also appear to interact with some of the serotonin and melatonin receptor subtypes.³¹

In a placebo-controlled clinical trial, the anti-depressant effect of hops or humulus in young people with minimal self-reported depressive and anxiety symptoms was investigated. Individuals in this trial were treated with hops capsules (2 capsules of 0.2 g once a day and once a night) in two 4-week periods separated by a 2-week washing period. They were asked to avoid products containing hops such as beer throughout the treatment. At the end of treatment, the results showed a significant reduction in depressive symptoms compared with placebo. However, the symptoms of depression in the participants of this trial were self-reported and research is needed to find out the effects of hops on actual depressed patients.³¹

2.10.2 Chamomile



Figure 28: [Chamomile. \(July 21, 2016\)](#)

Matricaria chamomilla or Chamomile is a medicinal plant containing compounds such as flavonoids (such as apigenin and luteolin), tannins, melatonin, volatile essential oils containing azulene and mucilage and other compounds. This medicinal plant has many properties and it is believed to have anti-anxiety and anti-depressant properties. Although the exact mechanism of chamomile is not known, some of its flavonoid compounds may exert their effects by modulating central noradrenaline, dopamine, serotonin and GABA.³²

To evaluate the antidepressant activity of chamomile, a randomized, double-blind, placebo-controlled study was performed on 57 adults with primary generalized anxiety disorder (GAD) with or without concurrent symptoms of depression and anxiety. Patients were divided into 3 groups: anxiety with comorbid depression, anxiety with a history of depression in the past, and anxiety without current or past depression. Treatment was increased to 1 capsule of 220 mg/day chamomile for the first week and then to 2 capsules in the second week. Then, if there is a decrease of more than 50% in total Hamilton score compared to baseline, does is increased to 3 capsules per day in the third week, 4 capsules per day in the fourth week and finally to 5 capsules per day in weeks 5 to 8 of treatment. The results showed a significant decrease in total HAM-D scores for chamomile compared to placebo and this decrease was greater in people with current comorbid depression than other groups. Therefore, in addition to its anti-anxiety effect, chamomile may also have an anti-depressant effect.³²

The effect of chamomile tea in another clinical trial on anxiety and depression in cancer patients has also been investigated. In this study, which was related to the chemotherapy

department of 22 Bahman Hospital in Neishabour, patients were divided into two groups: chamomile tea treatment (n = 55) and control group (n = 55). The treated group used chamomile tea once a day for two weeks and the results at the end of the treatment showed a reduction in depressive symptoms.³³

Variable		Mean experimental group	Mean control group	P-value
Anxiety	Before intervention	23.10	22.03	0.71
	After intervention	17.61	21.25	0.18
Depression	Before intervention	25.81	25.83	0.99
	After intervention	19.49	24.90	0.003

Table 13: Two-sample t-tests for outcome variables, experimental and control groups.³³

2.11 GinSin capsule



Figure 29: [GinSin Capsoule, Goldaru company](#)

Medicine name	GinSin
Name of manufacturer	Goldaru company
Dosage of drugs and active ingredients	250 mg of ginseng rhizome powder
Consumption instruction	Twice a day, 2 ginseng capsules after a meal, the treatment period should continue for at least 4 weeks.
Indications	Anti-anxiety and anti-depressant effects Helps to increase concentration and strengthen intellectual powers and enhance learning and memory Lowers blood sugar and strengthens the effect of insulin in the body Cholesterol lowering and intensifying vasodilation
Side effects	Complications such as high blood pressure, impatience, restlessness, insomnia, diarrhea and skin rash if consumed in excess

Drug Interactions	Not recommended for people with high blood pressure, acute infections and asthma, heavy menstrual bleeding, during pregnancy and lactation, as well as when taking anti-coagulants such as aspirin and heparin.
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Table 14: GinSin capsule, containing *Panax ginseng*

2.11.1 *Panax ginseng*



Figure 30: [Ginseng](#)

Panax ginseng is a medicinal plant whose roots contain compounds such as ginsenosides, fatty acids, polysaccharides, oligopeptides and polyacetylenic alcohol. The anti-depressant mechanism of this plant may be related to increased levels of serotonin, dopamine and norepinephrine or upregulation of BDNF.³⁴

A double-blind randomized clinical trial was performed on 383 postmenopausal women (193 people treated with ginseng and 191 people treated with placebo) to evaluate the anti-depressant effects of ginseng and the results showed that ginseng had a superior effect compared to placebo.³⁵

A study in mice found that total ginseng at doses of 50 and 100 mg/kg for 7 days reduced immobility time in the FST test, as well as reversed, decrease in locomotor activity and prolongation of latency of feeding in a new environment in a chronic stress model of depression in rats. Therefore, it seems that this plant may have anti-depressant effects, although more studies are needed.³⁶

Chapter 3: Interviews with Psychiatrists about Herbal Antidepressants

In this section, the results of interviews with 25% of psychiatrists in places like as four-way Taleghani, Azimieh, Mehrshahr, Jahanshahr, Golshahr and Shahin Vila, will be discussed in person and online. For this purpose, a questionnaire has been provided to them, which contains questions related to depression and herbal anti-depressants.

3.1 Questionnaire and results from interviews with psychiatrists

In this article, 25% of all psychiatrists in Karaj (80 people), ie 20 psychiatrists, were interviewed and given a questionnaire.

1) Do you prefer to use herbal medicines or synthetic medicines to treat depression?

100% of psychiatrists prefer to use synthetic drugs.

2) Do you use herbal medicines as the main treatment or treatment aid?

14 psychiatrists do not prescribe any herbal medicine and 6 people use herbal medicine as an aid to treatment.

3) Are the herbal medicines that you use as an adjunct treatment to improve the anti-depressant effects or for some other problems such as insomnia?

As mentioned, 70% of psychiatrists do not prescribe herbal medicine at all

30% are used both to improve the anti-depressant effects and to improve other problems

4) If you prescribe herbal medicines for patients with depression, what is the main reason?

A) Due to the introduction of manufacturing companies

B) Due to the introduction of pharmacies

C) Patients have had good experiences and transferred

D) because of their fewer side effects

E) Due to introduction in retraining courses

F) State your reason and give more details if you wish

As mentioned, 70% of psychiatrists did not prescribe herbal anti-depressants and 30% (6 out of 20) did. From the six psychiatrists who prescribed herbal medicine, 3 people (50%) believed that they had fewer side effects.

Two psychiatrists also stated that the patients had good experiences and transferred.

And one person believed that in some patients with mild depression who do not want to use synthetic drugs or the disease is not to the extent that a strong drug is needed, use herbal medicines.

5) If you do not prescribe herbal medicines for patients with depression, what is the main reason?

A) Unfamiliarity

B) Lack of scientific documentation

C) Lack of welcome for patients

D) Patients expect physicians to prescribe synthetic and prescription drugs, not those that can be purchased OTC.

E) Lack of scientific documentation on side effects and drug interactions

F) State your reason and give more details if you wish

From the 14 psychiatrists who did not prescribe herbal antidepressants, 29 percent agreed with the second option (B).

7% agreed with the fifth option.

Another 7% agreed with the fourth option

43% agreed with the first option

14% agreed with the first, second and fifth options.

Some reasons given by psychiatrists for not prescribing herbal antidepressants:

Some of them stated that herbal medicines are not very well defined in our pharmacopoeia and not all of them are FDA approved or have not been mentioned much in their textbooks and universities. But in some cases, mild to moderate depression can be used, but not routinely and continuously. Some have suggested that these drugs do not work in severe depressive disorders. Others thought that herbs did not have very strong effects, and in order to make them important, they turned them into herbal and commercial medicines.

6) Which herbal medicines do you prescribe?

Nervoxin, Perforan, Simosleep, Ginkogol, Ginkgo TD, SaffroMood and Ginsin

7) What percentage of your patients have received positive results from receiving herbal medicines?

None of them knew exactly.

8) Do you prescribe other OTC products such as omega 3 fatty acids, vitamins and other supplements for patients with depression?

85 percent of psychiatrists used supplements, but not as an anti-depressant, but as an adjunct to improve some functions.

3.2 Discussion

Depressive disorders are one of the main causes of global health burden, and in recent years, with the epidemic of Covid-19 and its consequences (such as social restrictions, closure of schools, universities and businesses, reduction of economic activities, increase of domestic violence, The increase in caregiving and domestic responsibilities of women and the reduction

of recreation and entertainment), the prevalence of this disorder has increased, especially in women and young people. Treatment of depression is very important like any other disease. This mental disorder not only disturbs a person's psyche, but it can also lead to physical diseases, turning to drugs and even suicide. Therefore, if the affected patients suffer unwanted side effects from the treatment apart from the disease, the situation is much more difficult for them and the treatment will be less effective.³

Based on the results of this article, it seems that herbal anti-depressants can be effective in treating mild to moderate depression. Although according to some clinical trials, the effectiveness of some herbs can be similar to some synthetic drugs (*Hypericum perforatum* similar to fluoxetine and imipramine-Saffron, Urtica, Lemon balm and lavender similar to fluoxetine), it should also be noted that in most In these trials, participants consisted of people with mild to moderate depression, and due to the high risk of severe depression for patients, it was not possible to evaluate the effect of herbal medicines in this area. Although the use of herbal medicines in the treatment of many disorders and diseases is progressing, there are still concerns about the appropriate dosage, drug interactions, side effects, and insufficient knowledge of their potential and exact mechanism.

Based on the results of trials reviewed in this article, it seems that most herbal medicines have a possible anti-depressant effect by modulating neurotransmitters (serotonin, dopamine, norepinephrine and GABA) or the antioxidant properties of their flavonoid compounds. It also seems that herbal medicines can be welcomed by many patients with depression such as pregnant women, people with cancer and postmenopausal women and people with difficult and special conditions in general due to less side effects. Unfortunately, due to the commercial form of drugs in Iran, some psychiatrists, prescribe only drugs introduced by pharmaceutical companies and pharmacies, and as a result, a limited number of known drugs for most of their patients, and for this reason, they are not familiar with some newer medicines, especially herbal medicines in different forms and brands, and they do not prescribe them routinely. It seems that in Iran, different pharmaceutical companies, by giving commissions to psychiatrists, encourage them to prescribe them while familiarizing them with herbal medicines. Therefore, in the first step, it is necessary to hold conferences on the review of herbal antidepressants for psychiatrists in different places of the country so that psychiatrists have a relative familiarity with these drugs so that they can, in the next steps, investigate these drugs further and perform controlled clinical trials with large and accurate samples. But in other countries such as America, the situation is not like this. In America, drug companies do not sell and cannot advertise or promote herbal medicines since they are not legally sold for any medical purpose. The world is moving towards herbal medicines and people in different countries with different cultures use herbal medicines, that's why this industry has a bright future.

3.2.1 Challenges

Communicating with and interviewing psychiatrists in Karaj was challenging because many psychiatrists were reluctant to fill out questionnaires for a variety of reasons. For example, some of them did not want to participate in research work and others did not have the opportunity to be interviewed in the office due to the high workload and the large number of their patients. Therefore, for interviewing some of them, like other patients, the previous time was taken and with others, communication was done virtually through Instagram.

3.3 Conclusion

According to the study of herbal anti-depressants of different pharmaceutical companies in Iran and the results of various trials conducted in the second chapter, herbal medicines seem to be effective in treating depression are Hypiran, Perforan and Nervoxin, Rose oral drop, Rocina, SaffroMood, Cephalum Urtica, Deproherb drop and capsule, Epion, Simosleep tablet, Lavender syrupe, Ginkogol and Ginkgo TD tablets and GinSin capsule. According to the discussion section and the data obtained from the third chapter, it seems that these herbal medicines are effective in treating mild to moderate depression, and it seems that among them, drugs such as Nervoxin, Perforan, Simosleep, Ginkogol, Ginkgo TD, SaffroMood and Ginsin are more likely to be effective in treating depression because in trials, the possible role of their depression has been mentioned and they are also prescribed by psychiatrists in Karaj. However, it is not certain that they can be effective in treating all types of depression. In Iran, herbal anti-depressants are used as adjunctive therapy and not as the main and routine treatment, and a lot of research is still needed to clarify their mechanism.

Although a number of side effects and drug interactions have been reported for anti-depressants, it seems that herbal treatments may have fewer side effects than synthetic drugs, and some of them may be as effective as synthetic drugs. Therefore, these advantages can lead to the substitution of herbal medicines instead of synthetic medicines in some, or at least pave the way for further research on these drugs.

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