

Saffrox™

affron® 28mg

The first effective
Multifunctional Antidepressant
without impact on
Sexual Function and Weight Gain

100%
NATURAL



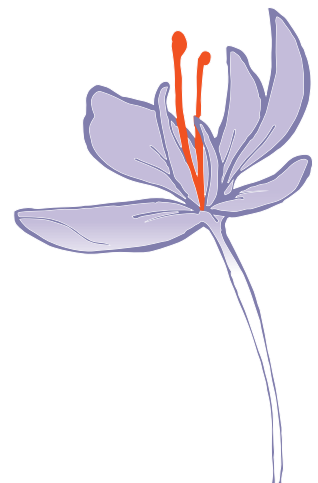


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affron® 28mg

The first effective
Multifunctional Antidepressant
without impact on
Sexual Function and Weight Gain

Target Group:

- As Mono-Therapy: Mild-Moderate MDD patients that cannot use antidepressant medication or those that refuse to take antidepressants.
- As Adjunctive: Noncompliance with the antidepressant treatment due to:
SSRIs, SNTIs induced Sexual Dysfunction.
- Patients with Subthreshold Depression.



The Need:

MDD patients that cannot use antidepressant medication or those that refuse to take antidepressants.

- 34% of the adults in the US used at least 1 unconventional form of health care 18
- In a Physician survey (Washington, New Mexico and Israel)- 60% recommend alternative medicine at least once in a preceding year (1994)¹⁹
- Reason why ²⁰:

Philosophical congruence: Alternative therapies are attractive because they are seen as more compatible with patients' values, worldview, spiritual/religious philosophy, or beliefs regarding the nature and meaning of health and illness.

Table 5.—Significant Predictors in the Multiple Logistic Regression (N=1035)

Variables	Adjusted Odds Ratio (95% Confidence Interval)	P
Education*	1.20 (1.10-1.31)	<.001
Health status*	1.32 (1.15-1.52)	<.001
“Cultural creative”	1.95 (1.43-2.67)	<.001
Holistic philosophy	1.42 (1.08-1.86)	<.02
Had transformational experience	1.76 (1.26-2.48)	<.005
Anxiety	3.13 (1.64-5.96)	<.001
Back problems	2.30 (1.66-3.20)	<.001
Urinary tract problems	2.16 (1.32-3.52)	<.005
Chronic pain	1.98 (1.13-3.48)	<.02

*These variables were coded on a 5-point Likert scale (all other independent variables were dichotomous).

the growing interest in alternative medicine may represent a type of cultural (Kuhnian³⁴) paradigm shift regarding health beliefs and practices

- With conditions like depression, for which several viable treatment options exist, patient attitudes and preferences are important and may have a large impact on patient adherence and subsequent recovery²¹

- **As Adjunctive: Noncompliance with the antidepressant treatment due to:**
 - **SSRIs, SNTIs induced Sexual Dysfunction.**

Antidepressant side effects are a common clinical challenge, often jeopardizing treatment adherence and quality of life ⁽¹⁷⁾ .

34% of SSRIs treated patients experiencing Sexual Function ADRs ⁽¹⁷⁾ adverse sexual effects - which can include loss of sexual drive, failure to reach orgasm and erectile dysfunction - are among the most common. While men are affected more often, women report more serious sexual side effects.

Saffrox[®] Positioning

To all Health Care Providers that treats Depressed patients, Saffrox is the first non Rx serotonin and dopamine enhancers combined with reduced float that offers effective Antidepressant treatment, without sexual dysfunction ADR, as a mono or adjunctive MDD treatment

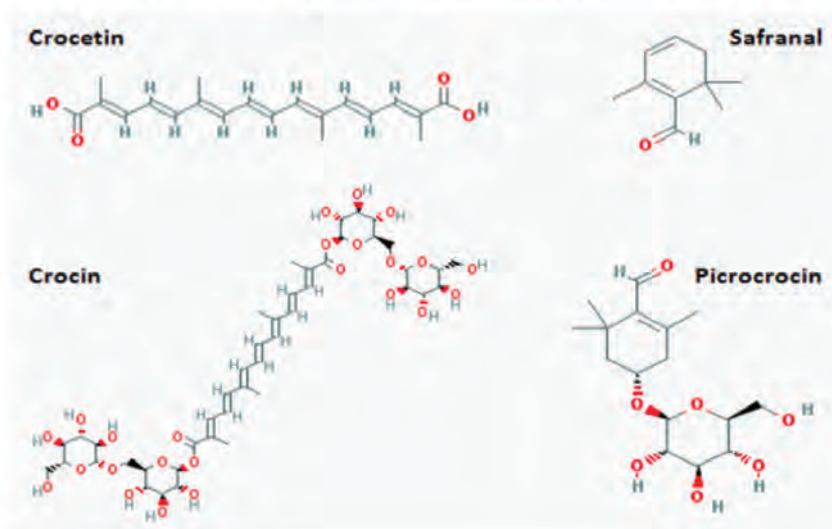
המרכיבים הפעילים ב-SAFFROX
affron [®] patented and standardized Saffron extract (Crocus sativus L.)
2% Crocin and 0.3% Safranal
MAGNOX [®] Magnesium oxide monohydrate
Curcumin extract
Piperine extract
Vitamin B6 (Pyridoxine hydrochloride)
Vitamin B12 (Cyanocobalamin)
Folic acid
L-methyl Folate - 5-Methyl Tetra Hydro Folate (5-MTHF)

Adding the accurate active ingredients of Saffrox:

Saffrox™ Major Components:

Saffrox™ contains affron®, patented standardized extract of the active pharmaceutical ingredients of saffron, containing high concentrate of Crocin (2%) and Safranal (0.3%).

Figure 1. Chemical composition of the most active constituents of saffron.



SPECIFIC MECHANISMS OF ACTION

affron®

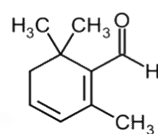
To help with Relaxation, Mental and Physical Balance, and maintain a Positive Mood

NMDA antagonism (BERGER et al., 2004)

GABA α agonism (Szafranski 2014)

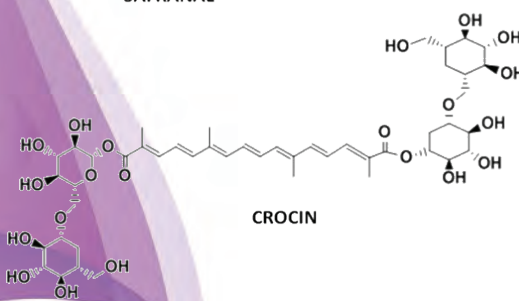
Brain-Derived Neurotrophic Factor (BDNF) activation (Hassani et al., 2004)

Main neurotransmitters related to mood and main Affron bioactive components:



SAFRANAL

Reuptake inhibition of Serotonin (Hosseinzadeh et al., 2004; Szafranski 2014)

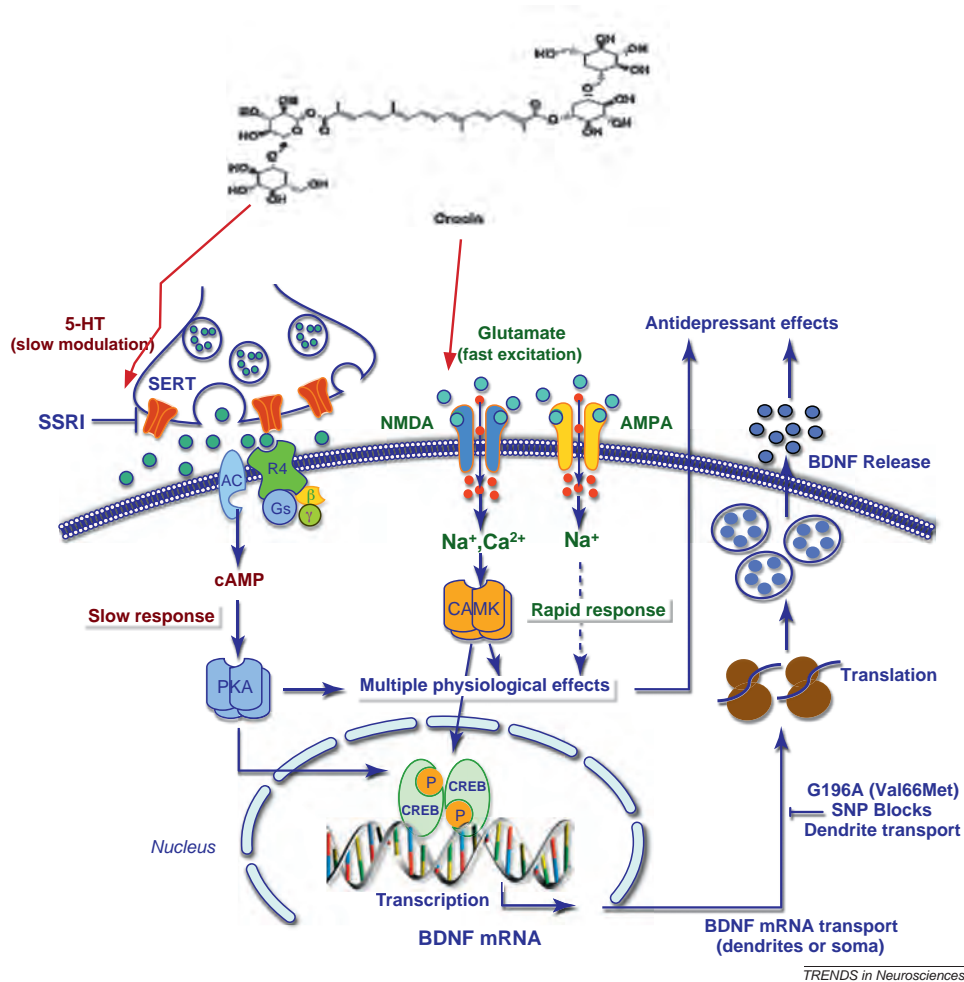


CROCIN



Uptake inhibition of dopamine and norepinephrine (Hosseinzadeh et al., 2004)

PHARMACTIVE
BIOTECH PRODUCTS
a natural difference

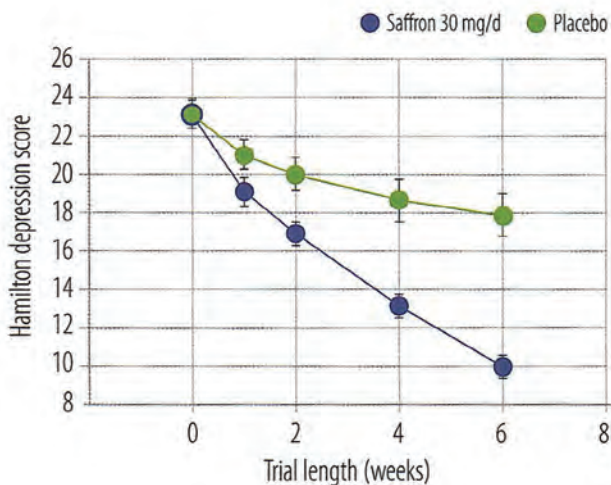


Saffron AD efficacy:

Efficacy established in Clinical Trials

Efficacy: RCT Placebo Controlled Trials:

Saffron extract compared to placebo



N = 40 Mild-Moderate

MDO

RCT DB.

Akhondzaden S, Tahmacebi-Pour N,

Noorbis AA et al. Phytother Res 2005

Figure. Fall in Hamilton depression score (HAM-D 17 items) when saffron extract is used instead of placebo. The participants in the saffron group scored significantly better after 6 weeks than the participants in the placebo group ($p < 0.001$).

RCT trial:

- ▶ Sixty adult patients with anxiety and Mild to Moderate MDD, were randomized to receive a 50 mg saffron or a placebo capsule twice daily for 12 weeks²².
- ▶ Saffron had a significant effect on the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) scores of subjects in comparison to placebo at the 12 week time-point ($p < 0.001$).

RCT trial:

- ▶ A double-blind, randomized trial of Saffron and placebo-controlled trial in the treatment of mild-to-moderate depression- N=40 patients²³.

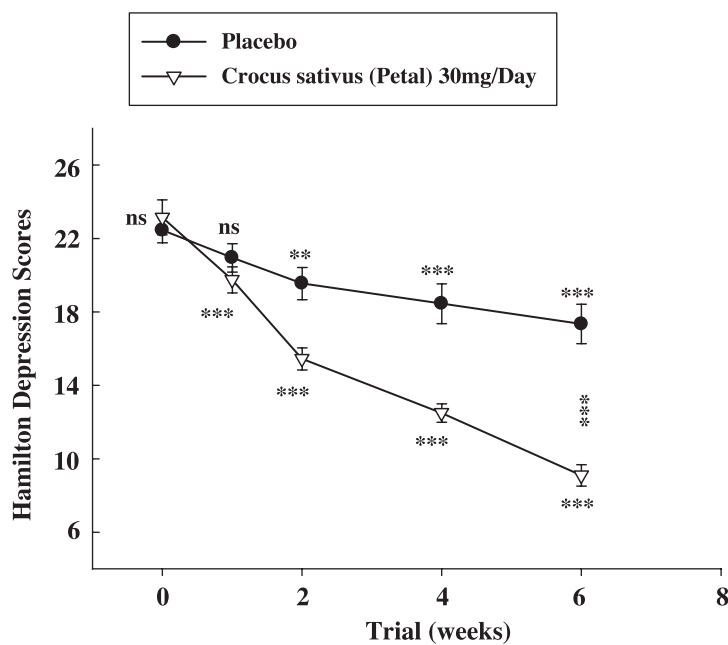


Fig.1 Mean 7 S.E.M. scores of two groups of patients on the Hamilton Depression Rating Scale. ns, non-significant, ** po 0.01 and *** po 0.001. The horizontal symbols (** and ***) were used to express statistical significance versus their respective baseline value and vertical symbol and ns were used for between-group comparisons.

Subthreshold Depression

RCT trial:

- ▶ In a 3 arm study, 128 participants self-reporting low mood but not diagnosed with depression, were given affron[®] at 28 mg/day, 22 mg/day, or a placebo treatment in a randomized, double-blind, placebo-controlled trial for 4 weeks²⁴.

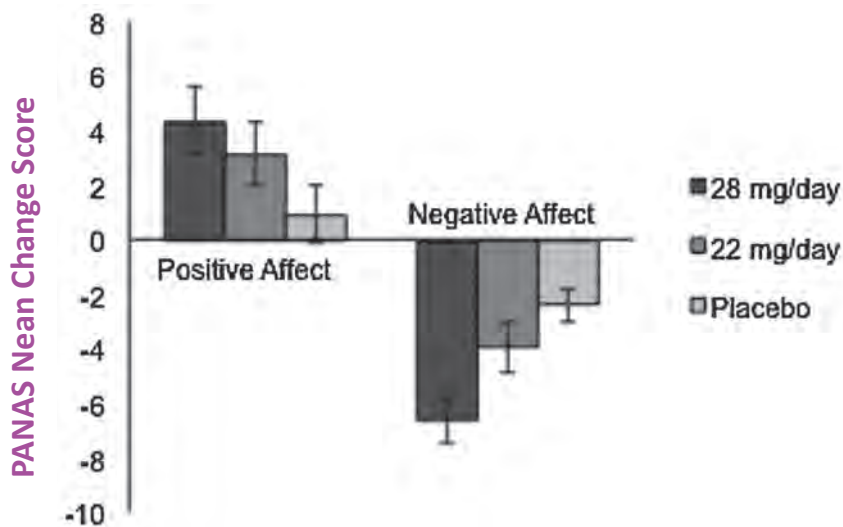


Fig.3 PANAS Mean change scores, subscales positive affect (PA) and negative affect (NA), after 4 weeks of treatment with 22 or 28 mg/day *affron*[®] or placebo.

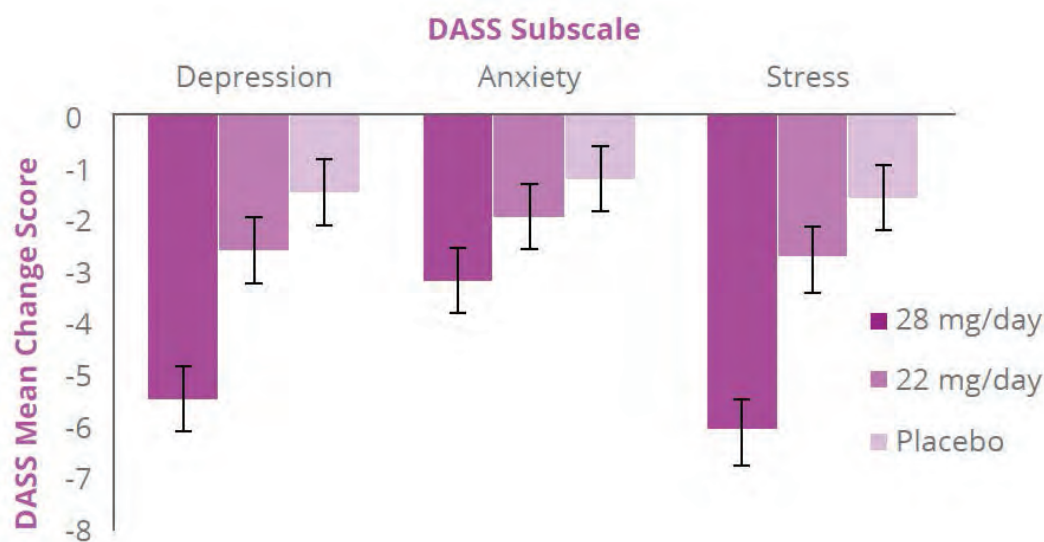


Figure 1. DASS mean change scores, subscales depression, anxiety and stress, after 4 weeks of treatment with 22 or 28 mg/day *affron*[®] or placebo

Saffron vs. Imipramine:

- ▶ In a RCT double-blind, single-center trial 30 mild to moderate MDD adult, receive capsule of saffron 30 mg/day (TDS) (Group 1) and capsule of imipramine 100 mg/day (TDS) (Group 2) for a 6-week study ²⁵.

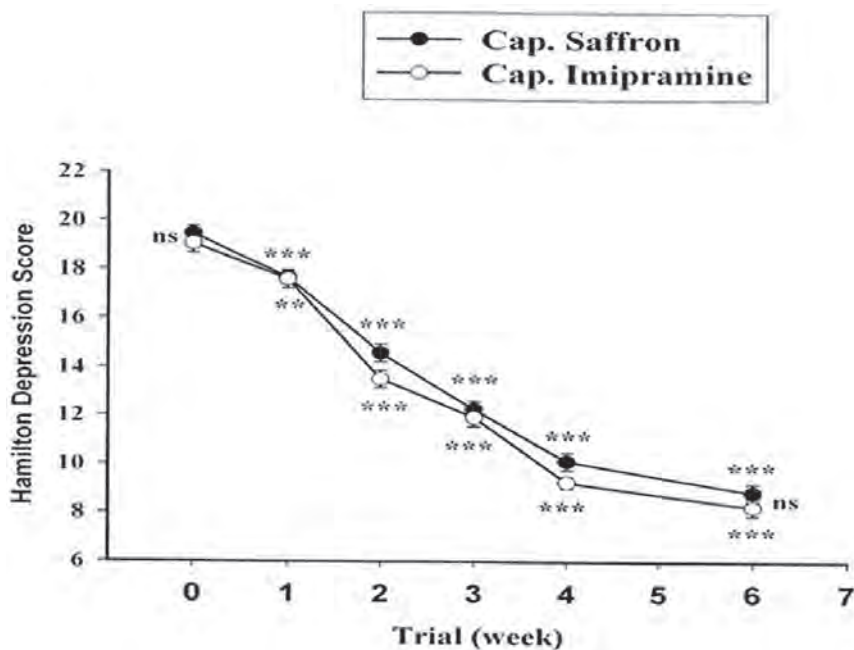


Figure 1
 Mean \pm SEM scores of two groups of patients on the Hamilton Depression Rating Scale. (ns) Non-Rating Scale. ns = non-significant, ** = $P < 0.01$ and *** = $P < 0.001$. The horizontal symbols (** and ***) were used to express statistical significance versus their respective baseline value and ns symbols are for between group comparisons.

Saffron vs. Fluoxetine:

Short-term therapy with saffron capsules showed the same antidepressant efficacy compared with fluoxetine⁶

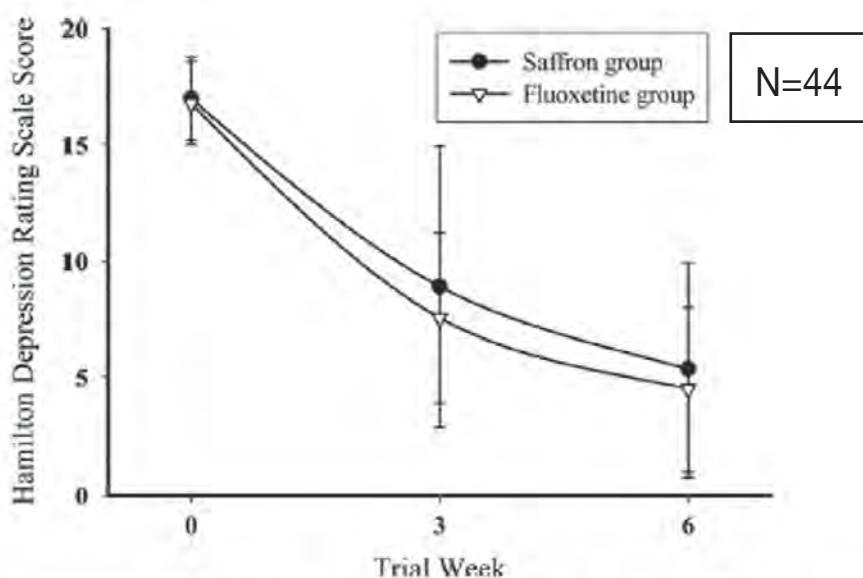


Fig. 2 Comparison of Hamilton depression rating scale (HDRS) scores [mean (SEM)] over time between the two study groups.

► In a TCT double blind trial, Saffron was found to be effective similar to fluoxetine⁷.

In a TCT double blind trial, Saffron was found to be effective similar to fluoxetine. N=40.

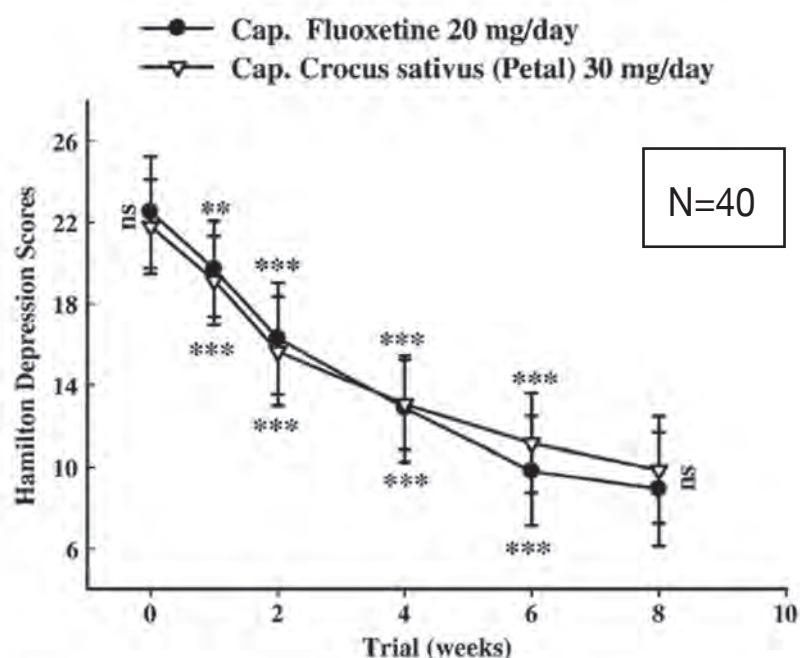


Fig. 1. Mean±S.E.M. scores of two groups of patients on the Hamilton Depression Rating Scale. ns = non-significant, **= $P < 0.01$ and ***= $P < 0.001$. The horizontal symbols (** and ***) were used to express statistical significance versus their respective baseline value and vertical symbols (ns) were used for between group comparisons.

Saffron in Mild to Moderate MDD –Metta Analysis:

A meta-analysis of randomized clinical trials-Findings from clinical trials conducted to date indicate that saffron supplementation can improve symptoms of depression in adults with MDD⁹ .

- Larger clinical trials, conducted by research teams outside of Iran, with long-term follow-ups are needed before firm conclusions can be made regarding saffron's efficacy and safety for treating depressive symptoms.

Saffron and Sexual Function Improvement:

- ▶ Reported frequencies of SSRI-induced sexual dysfunction have been between 7% and 70% (Fava and Rankin 2002; Hensley and Nurnberg 2002; Montejo-Gonzalez et al. 1997; Williams et al. 2006, 2010).
- ▶ Saffron is a tolerable and efficacious treatment for fluoxetine-related erectile dysfunction ⁽¹⁰⁾.

Psychopharmacology

N=30

Table 2 Comparison of changes in IIEF total and domains scores from baseline between the two groups

Week	Saffron group (mean±SD)	Placebo group (mean±SD)	Mean difference(95% confidence interval)	t(28), P value	Cohen's d (95% confidence interval)
Week 2, total	5.5±5.5	-1.1±9.5	6.6 (0.8 to 12.4)	2.325, 0.028	0.8(0.1 to 1.6)
Week 4, total	8.2±3.9	0.9±4.5	7.3 (4.1 To 10.4)	4.666, <0.001	1.7 (0.8 to 2.5)
Week 2, erectile function	2.2±1.1	-1.9±3.4	4.1 (2.2 to 6.0)	4.391, <0.001	1.6 (0.8 to 2.4)
Week 4, erectile function	4.5±2.5	-2.5±4.6	7.0 (4.2 to 9.7)	5.221, <0.001	1.9 (1.0 to 2.8)
Week 2, satisfaction with intercourse	1.4±1.8	-0.8±3.2	2.2 (0.3 to 4.1)	2.338, 0.027	0.8 (0.1 to 1.6)
Week 4, satisfaction with intercourse	2.1±1.6	-0.2±1.6	2.3 (1.1 to 3.5)	3.889, 0.001	1.4 (0.6 to 2.2)
Week 2, orgasmic function	0.7±1.4	0.1±1.3	0.7 (-0.3 to 1.7)	1.341, 0.191	0.5 (-0.2 to 1.2)
Week 4, orgasmic function	1.1±1.5	0.3±1.0	0.8 (-0.1 to 1.7)	1.727, 0.095	0.6 (-0.1 to 1.3)
Week 2, sexual desire	0.2±1.1	0.3±1.1	-0.1 (-0.9 to 0.7)	-0.167, 0.868	-0.1 (-0.8 to 0.7)
Week 4, sexual desire	0.5±1.7	0.2±1.0	0.3 (-0.7 to 1.4)	0.657, 0.517	0.2 (-0.5 to 0.9)
Week 2, overall satisfaction	0.7±1.5	0.7±1.0	0.1 (-0.9 to 1.0)	0.142, 0.888	0.05 (-0.7 to 0.8)
Week 4, overall satisfaction	1.2±1.7	0.7±1.2	0.5 (-0.6 to 1.6)	0.984, 0.334	0.3 (-0.4 to 1.1)

IIEF International Index of Erectile Function scale

Safrox extract Suppress sexual ADR of SSRIs in women:

- ▶ A RCT in 38 depressed women treated with Fluoxetine and suffers from sexual ADR randomly double blind assign to placebo or Saffron (2X15 mg/day ⁽¹⁶⁾.

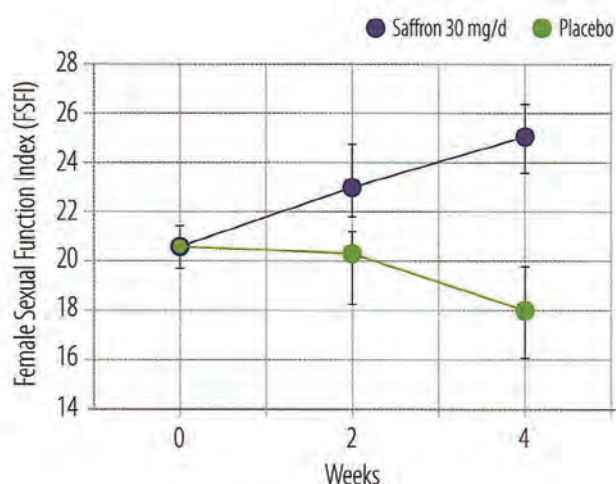
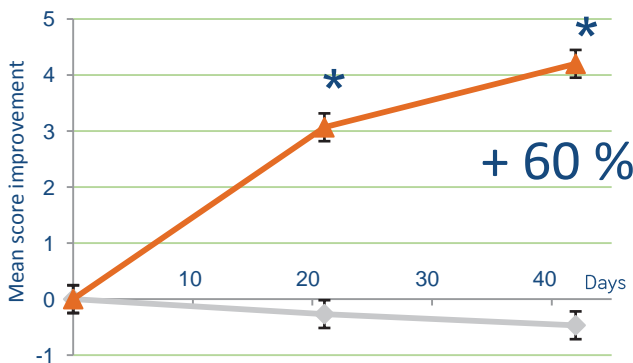


Figure. Improvement of sexual function in the use of saffron extract ($p < 0.001$), measured using the Female Sexual Function Index (FSFI, a 19-item questionnaire on

Saffrox Improves Sleep Profile in MDD

A double-blind randomized and placebo controlled clinical study was conducted in 2014 on 30 subjects. The efficiency was assessed using evaluation questionnaires.

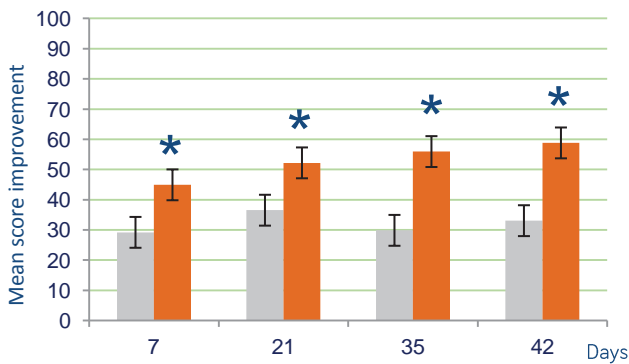
► Improvement of global sleep quality



Saffr' Activ[®] helps falling asleep, improve sleep quality and allows to wake up well rested.

Saffr' Activ[®] was found to improve significantly the global sleeping quality in 100% of the subjects.

► Improvement of fatigue condition



► Improvement of mood

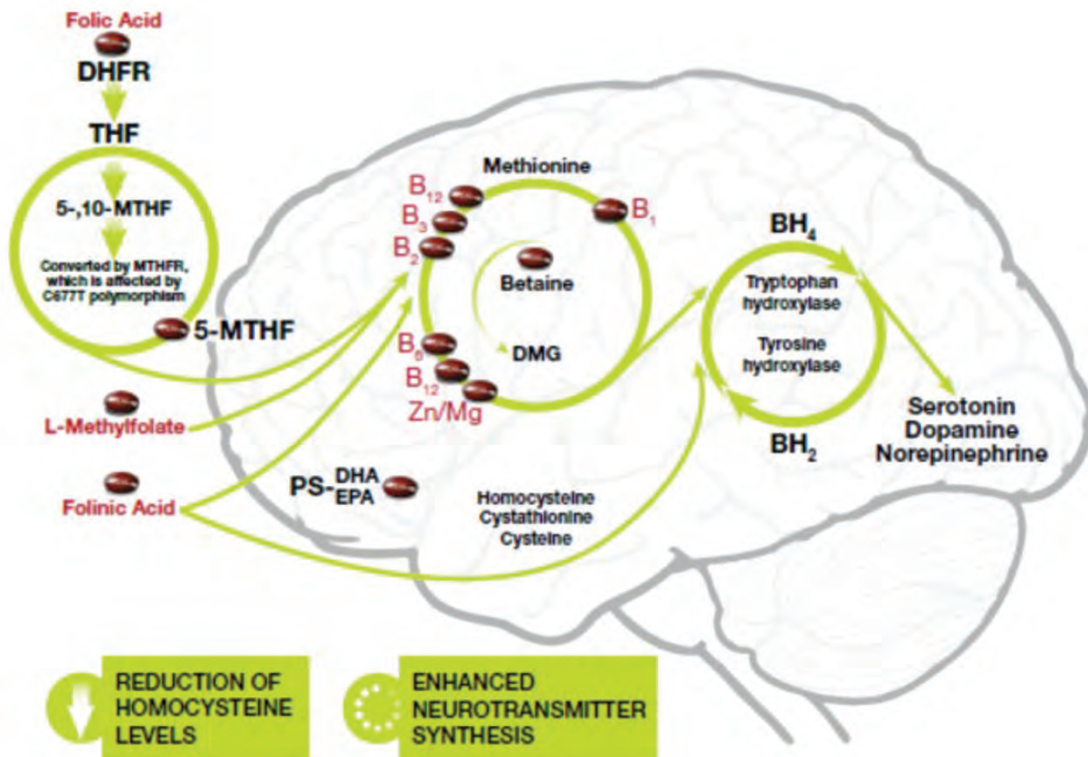
► Improvement of mental acuity

Subjects in Saffr' Activ[®] group felt significantly less tired than the placebo group, from the first week of treatment.

- Placebo
- Saffr' Activ[®] (30 mg/day)
- * Significant difference p<0.05

Folate

Mode of Action:



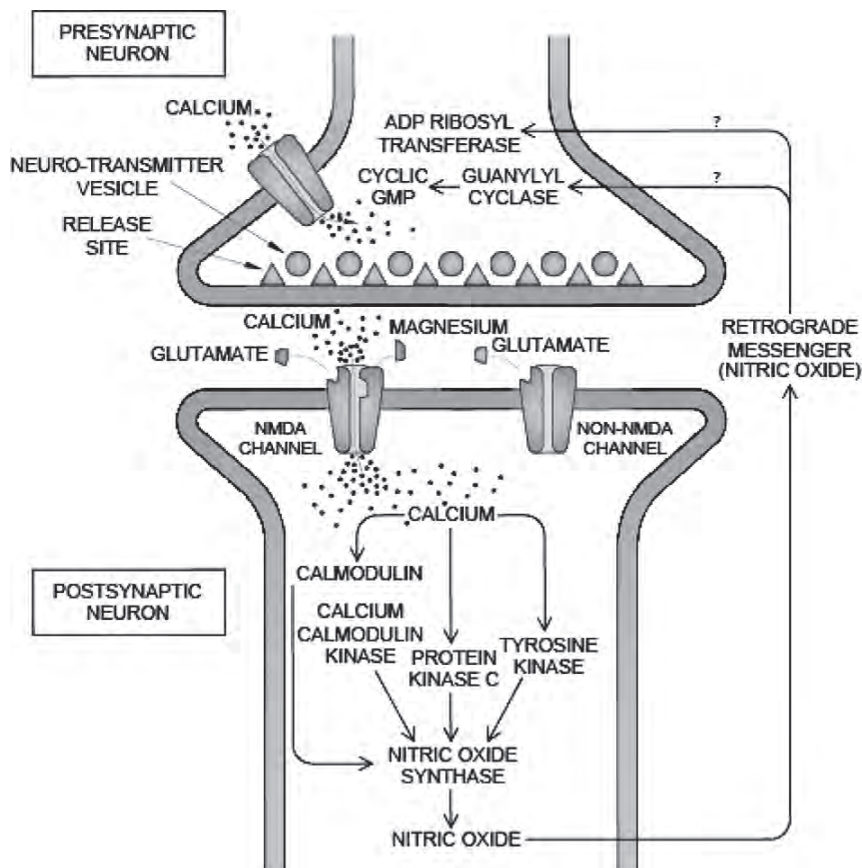
L-Methyl-Folate Efficacy:

C677T polymorphism - 60% of the U.S. population, might be associated with increased risk of depression due to 5-MTHFR insufficient activity ⁽¹¹⁾.

Efficacy:

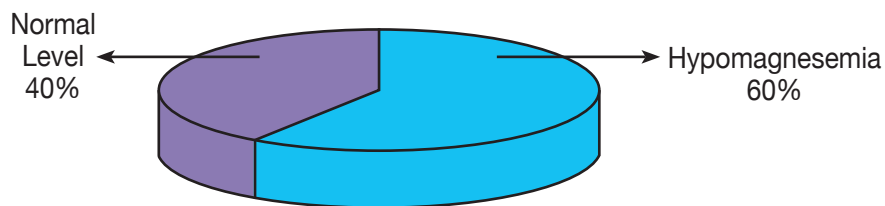
- ▶ Among depressed patients methylfolate significantly improved clinical and social recovery at 3 months ($P < .02$) and 6 months ($P < .01$) compared to patients treated with antidepressants and placebo effect ⁽¹²⁾.
- ▶ 5'-MTHF and Trazadone are equally effective in improving depressive symptoms in patients with mild to moderate dementia ⁽¹³⁾.
- ▶ L-Methyl Folate significantly improved depressive symptoms based on the HAM-D scale with the majority reporting improved mood and less fatigue ($P < .01$) ⁽¹⁴⁾.

Magnesium



60% of Israelis are Magnesium deficient

על פי מחקרים שנעשו על ישראלים צעירים בריאים לכ-60% חסר בגנזיום¹



מרכז מידע ומחקר של הכנסת מגנזיום, צריכתו, תפקידיו וחשיבותו 15.03.2004

- ▶ Daily consumption of 500 mg magnesium oxide tablets for ≥ 8 wk by depressed patients suffering from magnesium deficiency leads to improvements in depression status and magnesium levels ⁽¹⁵⁾.

Short Communications

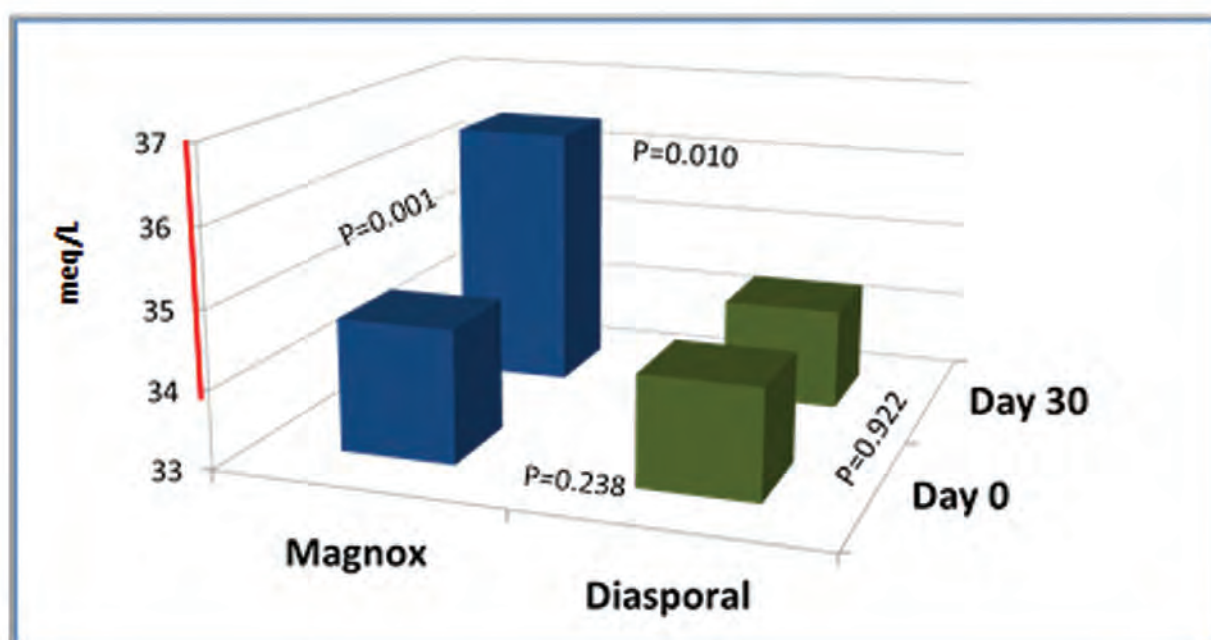
Association between Serum Magnesium Levels and Depression in Stroke Patients

Yingying Gu, Kai Zhao, Xiaoqian Luan, Zhihua Liu, Yan Cai, Qiongzhang Wang, Beilei Zhu*, Jincai He*

Table 2. Magnesium levels tertiles of patients

	Non-PSD (n=150)	PSD (n=59)	<i>p</i>
Mg ²⁺ category, n (% of total population)			0.013
Low tertile (≤0.84mmol/L)	45(30.0%)	30(50.8%)	0.005
Intermediate tertile (0.85-0.89 mmol/L)	59(39.3%)	19(32.2)	0.337
High tertile (≥0.90mmol/L)	46(30.7%)	10(16.9%)	0.044

Intracellular Magnesium



Normal range [Mg]_i = 33.9-41.9 meq/L





Key Messages:

- ▶ **Saffron** supports mood balance by regulating serotonergic, dopaminergic and glutaminergic Systems.
- ▶ **Saffron** suppress SSRI's sexual ADR that might increase treatment adherence.
- ▶ **Saffrox™** contains patented standardized afron® saffron pharmaceutical grade active ingredients in all batches (2% Crocin and 0.3% Safranal)
- ▶ **Saffrox™** the only preparation contains active (reduced) form of Folic Acid (L-Methyl Folate) that contribute to the production of Serotonin, Noradrenaline and Dopamin supporting mood balance.
- ▶ **Saffrox™** contains the most bioavailable patented Magnesium (Magnox™) for better CNS physiological function in Hypomagnesemic patients
- ▶ **Saffrox™** contains Turmeric aids mental balance and supports cerebral function
- ▶ **Saffrox™** contains Folic Acid, Vitamin B₆ & B₁₂ contribute to normal psychological functioning and reduces fatigue.
- ▶ High Safety Profile.

Applications:

- ▶ Support to mood balance
- ▶ Positive impact on sex life and sexual function (men and women)
- ▶ Resistance to mental stress
- ▶ Support to quality of sleep

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* התכשיר הינו תוסף תזונה ללא התוויות רפואיות.



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