

WHITE  
PAPER\*

# HOW SAFFRON CAN HELP RELIEVE PMS





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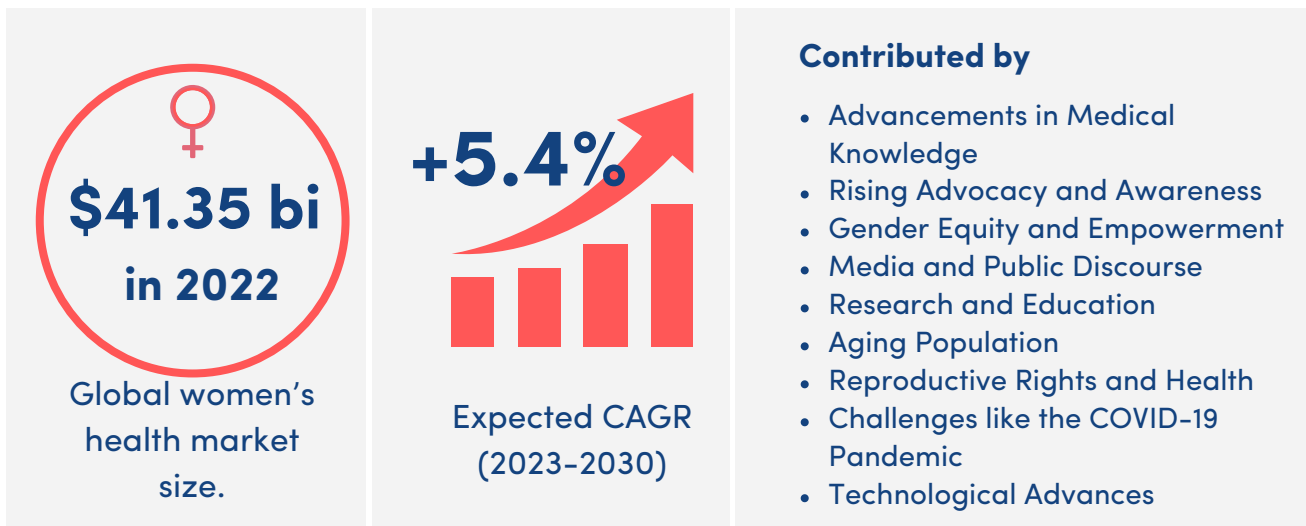
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# OVERVIEW OF WOMEN'S HEALTH: FOCUS ON PREMENSTRUAL SYNDROME

By Activ'Inside

## A GROWING MARKET

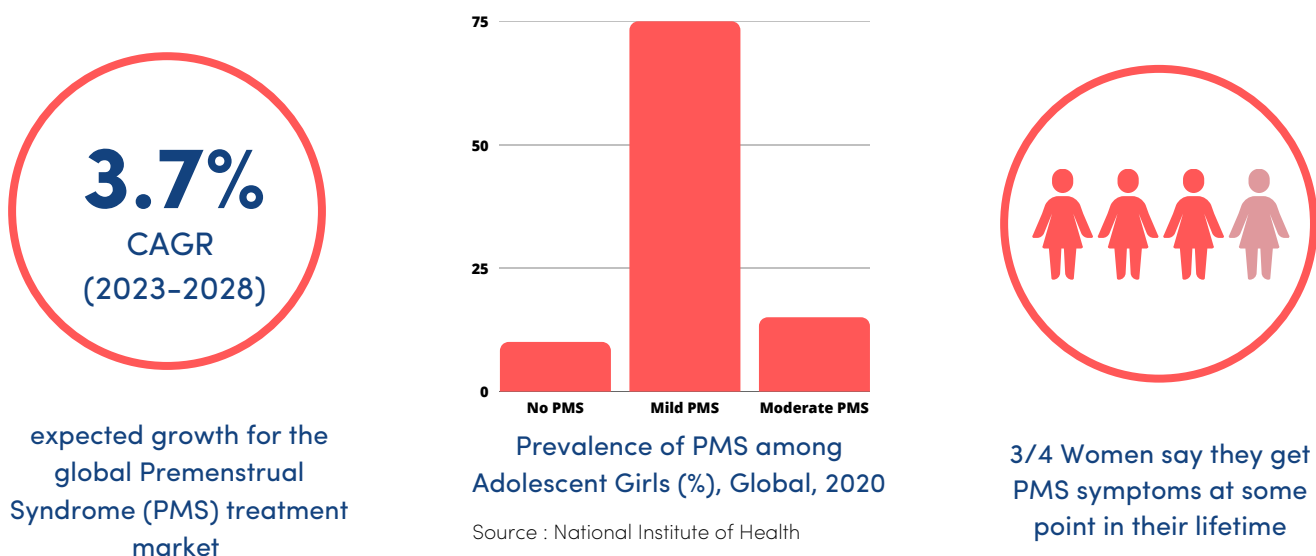


## A MARKET OF ITS OWN : PMS

In the realm of women's health, a distinct and significant market has emerged that addresses a common yet often overlooked aspect of many individuals' lives: Premenstrual Syndrome (PMS).

This market, characterized by a range of solutions aimed at alleviating the symptoms of PMS, reflects the growing recognition of the unique health needs and challenges faced by menstruating individuals.

As awareness about women's health continues to expand, the PMS market has carved out its own niche within the broader landscape.



# OVERVIEW OF PREMENSTRUAL SYNDROME

## DEFINITION OF PMS & SYMPTOMS

Premenstrual syndrome (PMS) is a cyclical disorder that occurs for many women before menstruation. Around 60% of women in childbearing age worldwide report PMS symptoms.

This trouble is characterized by physical and emotional symptoms that arrive 2 to 7 days before menstruation (sometimes up to 14 days) and end with the arrival of menstruation or within a few days of it.

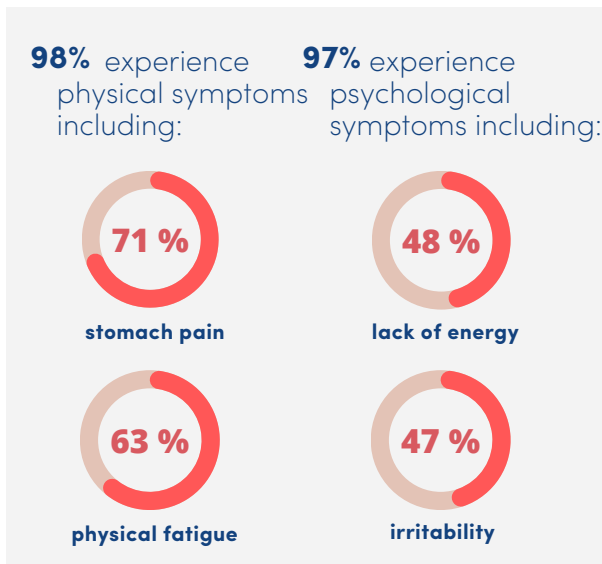
5% to 8% of women have a more severe form of PMS that can cause significant distress and functional impairment: premenstrual dysphoric disorder (PMDD).

PMS is linked to ovulation and menstrual cycle. It occurs mainly as a result of irregular fluctuations in the menstrual cycle: when oestrogen secretion decreases, progesterone secretion increases, then decreases in turn in the absence of pregnancy.

Fluctuations in **serotonin** levels can contribute to PMS symptoms such as irritability, anxiety, emotional imbalance and sleep disturbances.

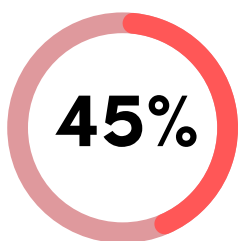
**Studies suggest that an imbalance in serotonin levels, particularly a decrease in serotonin levels, may be associated with an increase in PMS symptoms.**

Other factors may also contribute to PMS, such as stress, smoking, nutritional deficiencies or other diet (excessive sodium, alcohol, caffeine...).



“  
For **64%** of women, PMS interferes with their daily life  
”

## COMMON REMEDY WITH ONLY ONE TARGET



Women worldwide were self-medicated and taking analgesics to relieve the pain associated with premenstrual syndrome.

Drugs like analgesics are commonly used ease physical symptoms of PMS like cramps and headaches. However, they may not be the best long-term solution due to potential side effects from prolonged use.

As awareness of holistic care increases, people are showing more interest in alternative treatments like lifestyle changes, herbal supplements, and hormonal therapies. These options aim to address the multifaceted nature of PMS and offer more sustainable and effective relief for those dealing with this condition.

# WHO IS CONCERNED?

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## 1 BRITNEY, 19 YEARS-OLD

**PMS ISSUES** Every month, Britney experiences discomfort due to PMS. She suffers from severe cramps and bloating, making it difficult for her to focus on her studies or participate in her favorite activities. Emotional symptoms like stress and irritability also affect her relationships with friends and often prevent her from concentrating on her coursework.

**NEEDS** Relieve physical and emotional symptoms to be focus on studies & maintain her social life



## 2 SANDY, 32 YEARS-OLD

**PMS ISSUES** Since her late 20s, Sandy's PMS symptoms have become increasingly uncomfortable. She experiences physical and psychological symptoms such as legs discomfort, fatigue and nervousness. These symptoms often interfere with her productivity at work and make it difficult for her to keep up with her children's active schedules.

**NEEDS** Alleviate PMS symptoms to live her working life with peace of mind and enjoy her children to the full



## 3 ZORANA, 45 YEARS-OLD

**PMS ISSUES** Zorana's PMS symptoms have intensified as she approaches menopause. She becomes extremely irritable and sensitive, and feels that her weight varies greatly with her menstrual cycle. She also struggles with low energy levels and severe water retention especially in her legs, making it challenging for her to maintain her usual level of productivity.

**NEEDS** Prevent the imbalance associated with the arrival of her cycle

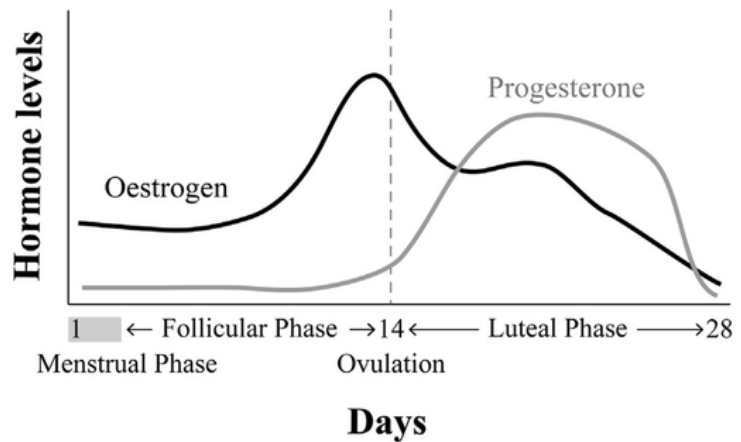
# MECHANISMS INVOLVED IN PMS

## HORMONAL CHANGES & SEROTONIN DYSREGULATION

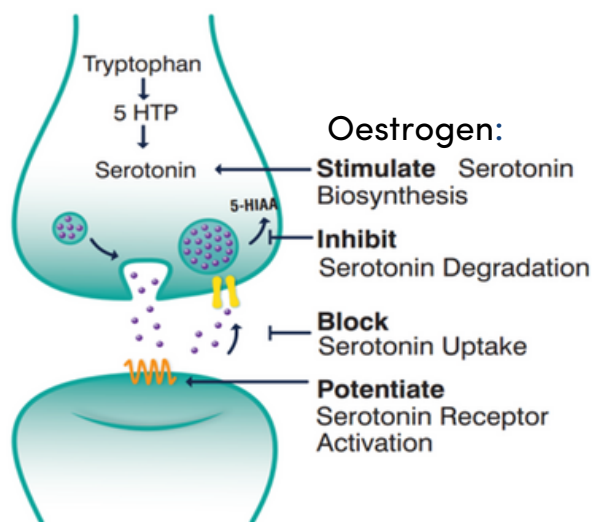
### Menstrual cycle & hormonal fluctuations

In the late luteal phase, around 7 days before the end of the cycle, progesterone & oestrogen levels drop.

In particular, this decrease in oestrogen has been associated with serotonin dysregulation & emotional imbalance.



### Oestrogen & serotonin transmission



Oestrogen favors serotonin transmission, by limiting its reuptake & degradation, while potentiating its receptor.

In the late luteal phase, the drop of oestrogen induces fluctuations in serotonin levels that can contribute to PMS symptoms such as irritability, nervousness, emotional imbalance and sleep disturbances.

A recent study found that shortly before menstrual onset, the serotonin-transporter in the brain is increased and thus promotes a synaptic loss of this neurotransmitter in women with PMDD. This finding can explain the symptoms in the affected women.

"PMS is closely associated with emotional imbalance through oestrogen-serotonin regulation."

# SAFFRON & PMS

## TRADITIONAL USE THROUGHOUT THE WORLD

Saffron has been used for mental well-being for thousands of years. In Persian Culture for example, saffron was used to treat menstrual disorders, muscular spasms and pain.

In ancient Egypt, Cleopatra used saffron to infuse her bath for aphrodisiac effects and created the kyphi, a fragrance had "the power to lead to sleep, illuminate dreams, ease the tensions of daily anxiety by bringing calm and tranquility to all who breathe it".



Used for more than 3000 years without side effects, Saffron benefits on both emotional and physical PMS symptoms are mentioned in the WHO monograph and in the Chinese pharmacopeia.



### World Health Organization

Health Canada

European Food Safety Authority (EFSA)

"Contributes to emotional balance"  
"Helps to support the relaxation"  
"Helps to maintain a positive mood"  
"Helps to maintain good comfort before and during menstrual cycle" \*

\*EFSA pending claims

Chinese Pharmacopeia

Traditional Iranian Medicine

Ayurvedic Medicine

Ancient Egypt Medicine

# SAFFRON & PMS

## CLINICAL EFFICACY

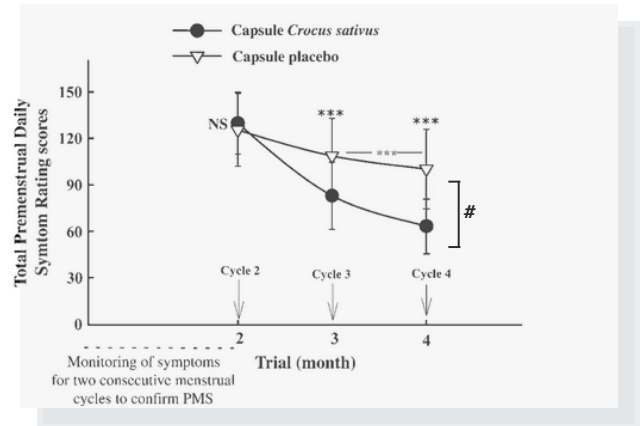
In the literature, 3 clinical studies investigate saffron's benefits on women suffering from PMS:

**Design:** randomized, double-blind, placebo-controlled study

<ul style="list-style-type: none"> <li>30mg Saffron extract (2% safranal UV)</li> <li>Placebo</li> </ul>	<ul style="list-style-type: none"> <li>50 women (20-45 yo)</li> </ul>	<ul style="list-style-type: none"> <li>2-month supplementation</li> </ul>
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### Results

- 30mg of saffron extract significantly decreases physical and emotional symptoms after 1 month of supplementation
- Saffron extract supplementation decreased the severity of PMS by 50% in 76% of supplemented women



Mean total PMS daily scores of women supplemented with saffron or placebo.

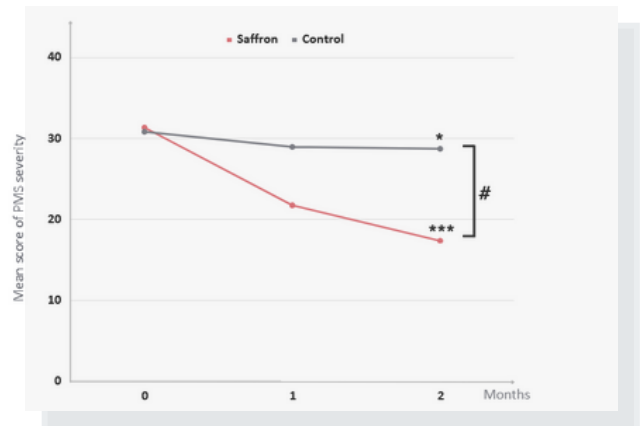
NS: non-significant; \*\*\*: P< 0.001 significance vs respective baseline value, #: P<0.001 significance between groups

**Design:** randomized, double-blind, placebo-controlled study

<ul style="list-style-type: none"> <li>30mg Saffron extract (2% safranal UV)</li> <li>Placebo</li> </ul>	<ul style="list-style-type: none"> <li>78 women (18-35 yo)</li> </ul>	<ul style="list-style-type: none"> <li>2-month supplementation</li> </ul>
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### Results

- 30mg of saffron extract significantly decreases physical and emotional symptoms after 2 months of supplementation compared to the placebo



Mean score of PMS severity of women supplemented with saffron or placebo.

\*: P>0.05, \*\*\*: P< 0.001 significance vs respective baseline value; #: P<0.001 significance between groups

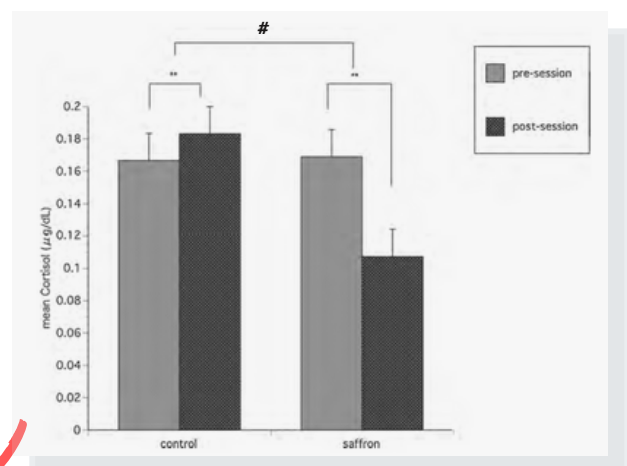
**Design:** randomized, double-blind, placebo-controlled study

<ul style="list-style-type: none"> <li>20-min stimuli</li> <li>Saffron odor</li> <li>Placebo</li> </ul>	<ul style="list-style-type: none"> <li>35 women (19-26 yo)</li> </ul>
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### Results

- Saffron odor significantly decreases the levels of salivary cortisol, the "stress hormone"

“ Saffron odor is due to its volatile molecules; mainly safranal ”



Mean cortisol concentration in 35 women supplemented with saffron or placebo.

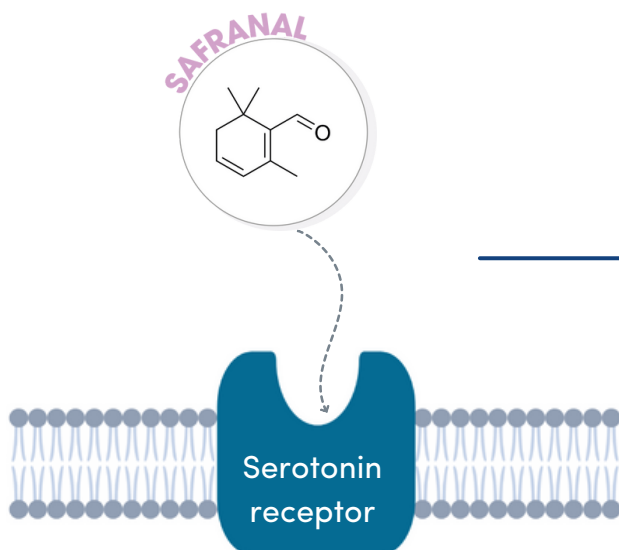
\*\*\*: P< 0.01 significance vs respective baseline value, #: P<0.01 significance between groups



# MAIN KEY-MOLECULE: SAFRANAL

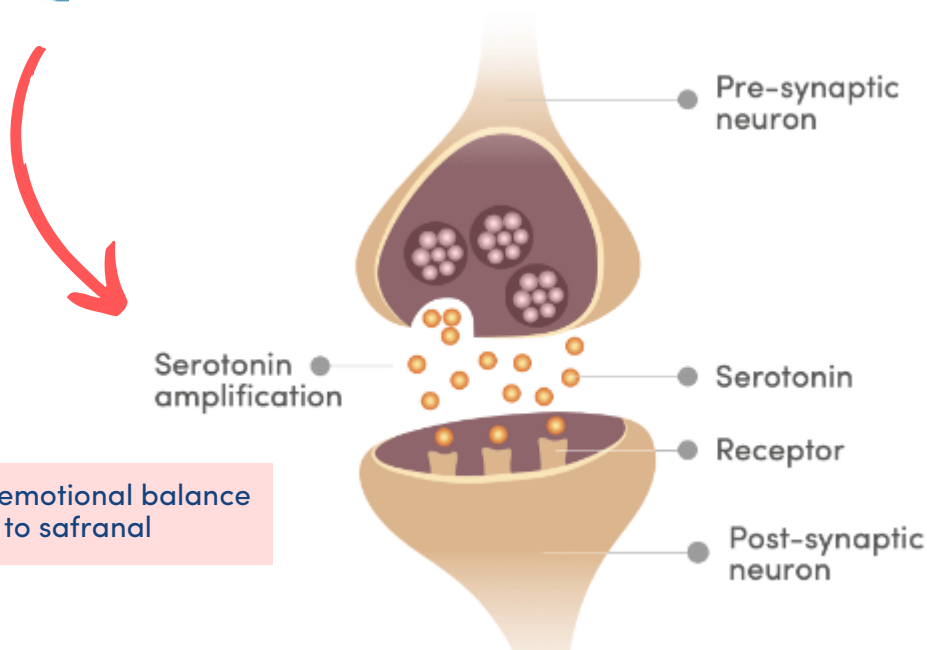
## ACTION ON SEROTONIN

Safranal, the main volatile compound in saffron, is the cause of its typical odor. It is the most described molecule for its action on serotonin, the "happiness neurotransmitter".



### Interaction between safranal & serotonin receptors

In silico study predicted that safranal can interact with two of the essential serotonin receptors in their putative ligand-binding site: 5HT1AR & 5HT2AR



Better emotional balance thanks to safranal

“  
Most of the saffron extracts are standardized at 2% safranal UV  
”

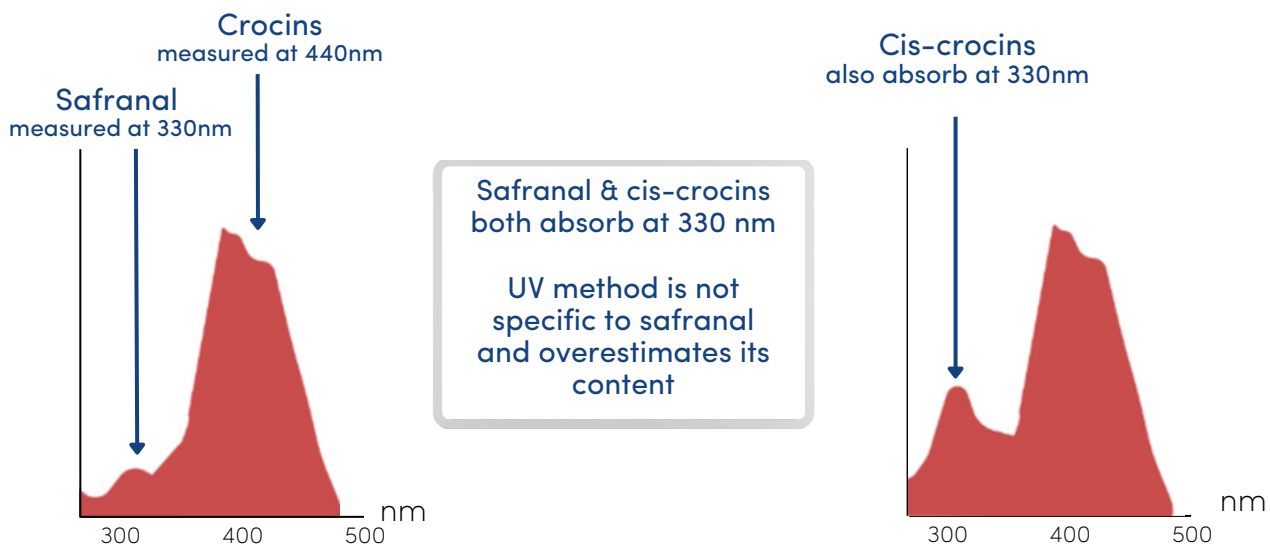
## ARE THEY REALLY EQUAL?

# MAIN KEY-MOLECULE: SAFRANAL

## OVERESTIMATED BY UV METHOD

### UV or ISO3632 standard method

Standard international method used for safranal quantification. This method quantifies the metabolites present in saffron according to the wavelength they absorb. In the case of safranal, absorbance is measured at 330nm.



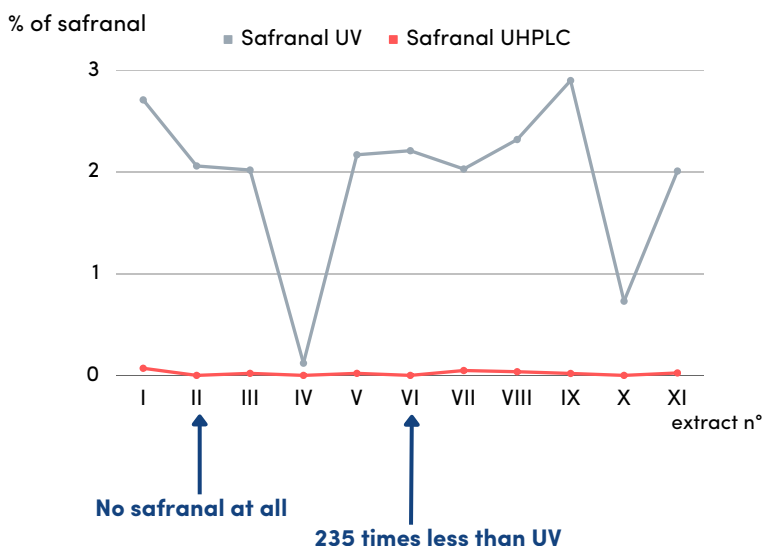
Saffron UV spectrum presented in ISO3632 method

Cis-crocins spectrum: absorption at 330nm

### HPLC method

High Pressure Liquid Chromatography is an analytical technique that separates and characterizes saffron metabolites based on their chemical and physical properties. HPLC is the only analytical method allowing a precise quantification of safranal. UHPLC, performed at higher pressure, is the state-of-the-art method, allowing a faster analysis.

### % of safranal in 12 extracts claiming 2% safranal UV measured by UV & UHPLC



### CONCLUSION

Very few/no safranal found in extracts standardized at 2% safranal UV

No correlation between UV & UHPLC method

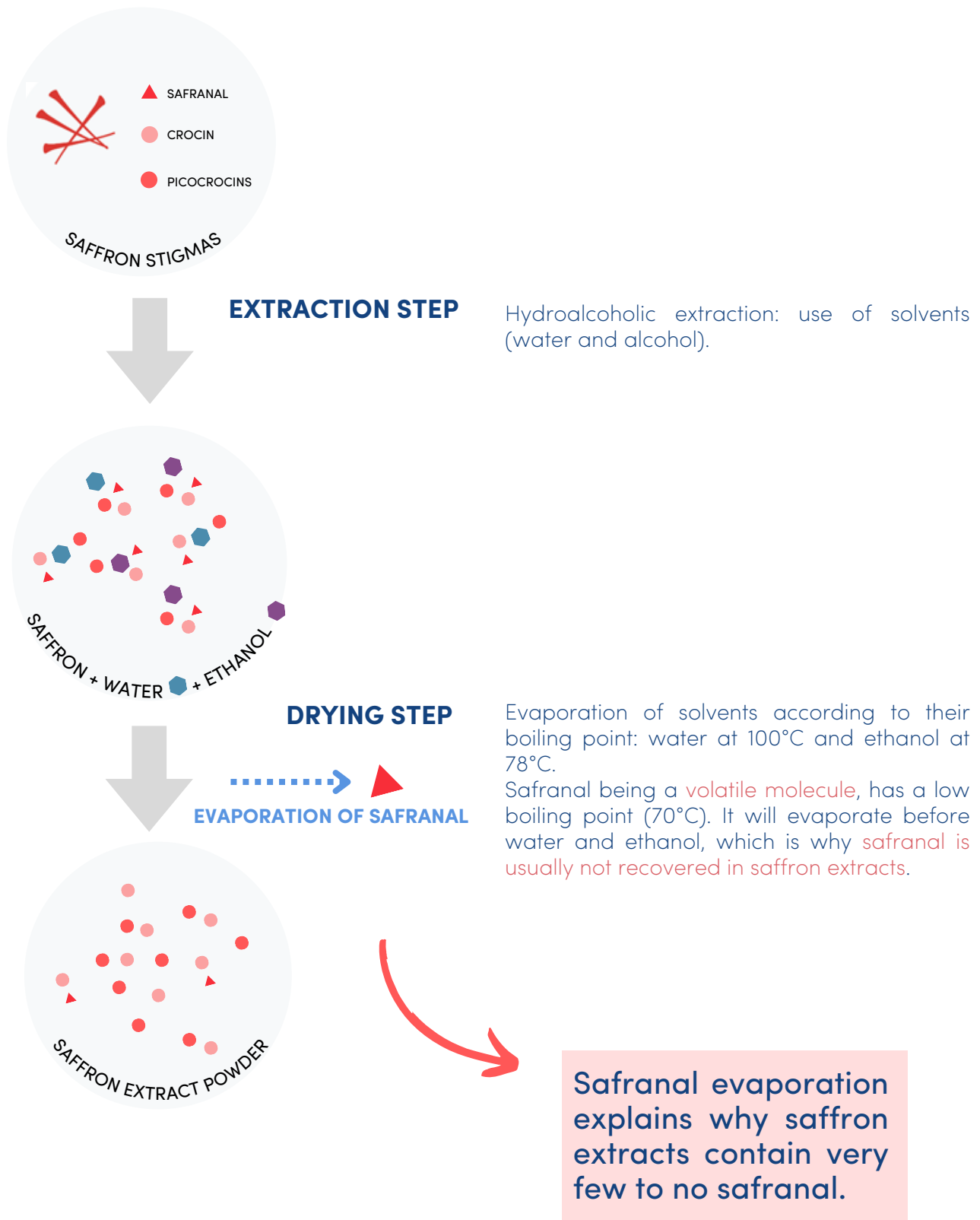


Both methods are needed for a precised knowledge of the extract. UHPLC is particularly needed for an accurate safranal quantification

# MAIN KEY-MOLECULE: SAFRANAL

## USUALLY LOST DURING THE EXTRACTION PROCESS

Classic process to obtain a dry saffron extract:



# SAFR'INSIDE™ : THE RICHEST SAFFRON EXTRACT IN SAFRANAL

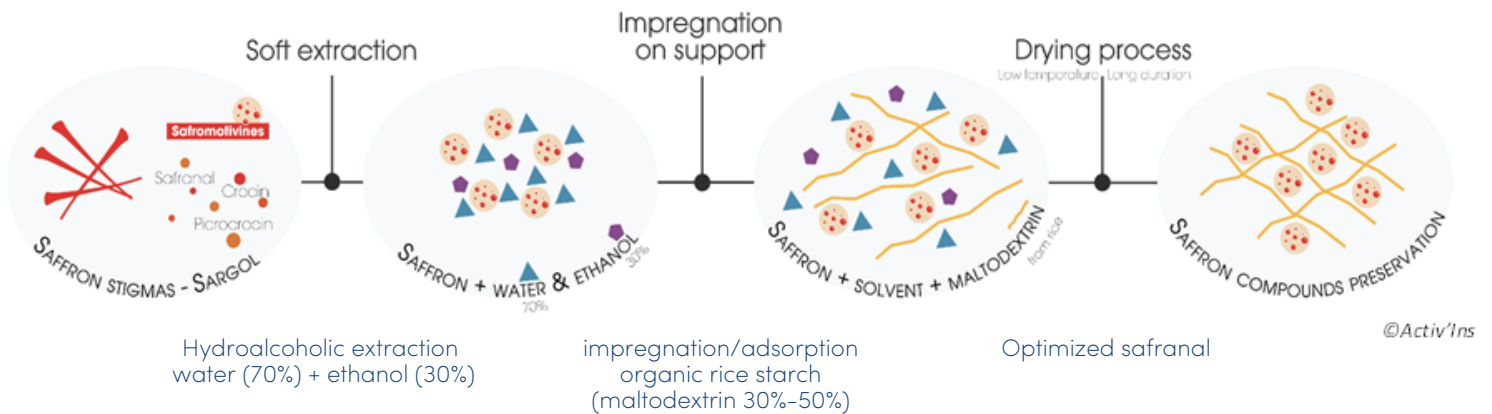
## TECH'CARE™ EXTRACTION PROCESS

Safr'Inside™ is the saffron extract with the highest safranal UHPLC content (a). Moreover, its extraction process preserves the full profile of the saffron, guaranteeing all its benefits (b).

This extraction process, called Tech'Care™, is inspired by ancestral recipes which, despite cooking at 100°C, naturally preserve all the saffron's aromatic profile, including its typical scent due to safranal.

### Tech'Care™ extraction process

Patented worldwide, this extraction process includes impregnation/adsorption of saffron metabolites in a matrix of rice starch thus preserving them from heat and solvent alterations.

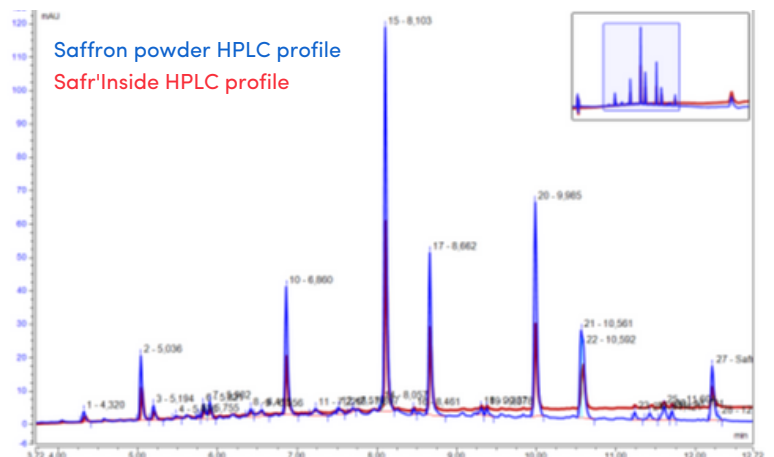


### a. Richest in safranal UHPLC

% of safranal in Safr'Inside™ and in 5 other saffron extracts on the market		
Extract n°	UV method	UHPLC method
I: Safr'Inside™	2%	0,2%
II	2%	0,03%
III	2%	0,05%
IV	2%	0,01%
V	2%	0,03%
VI	2%	0,011%

INTERNAL RESULTS

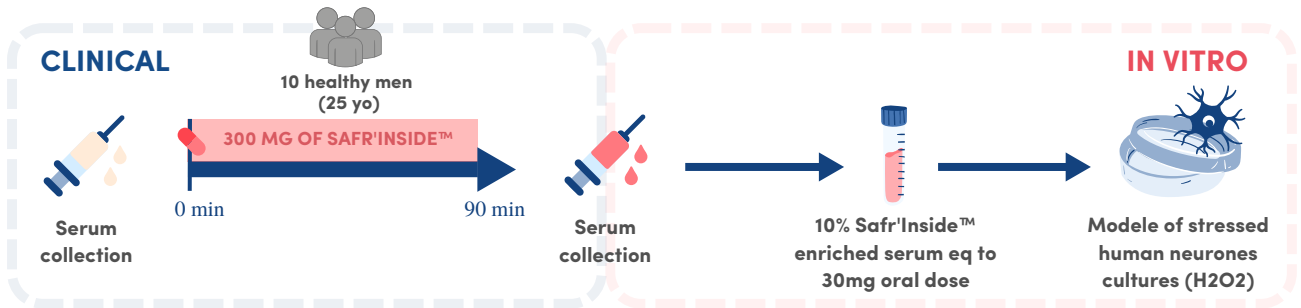
### b. Full spectrum saffron extract



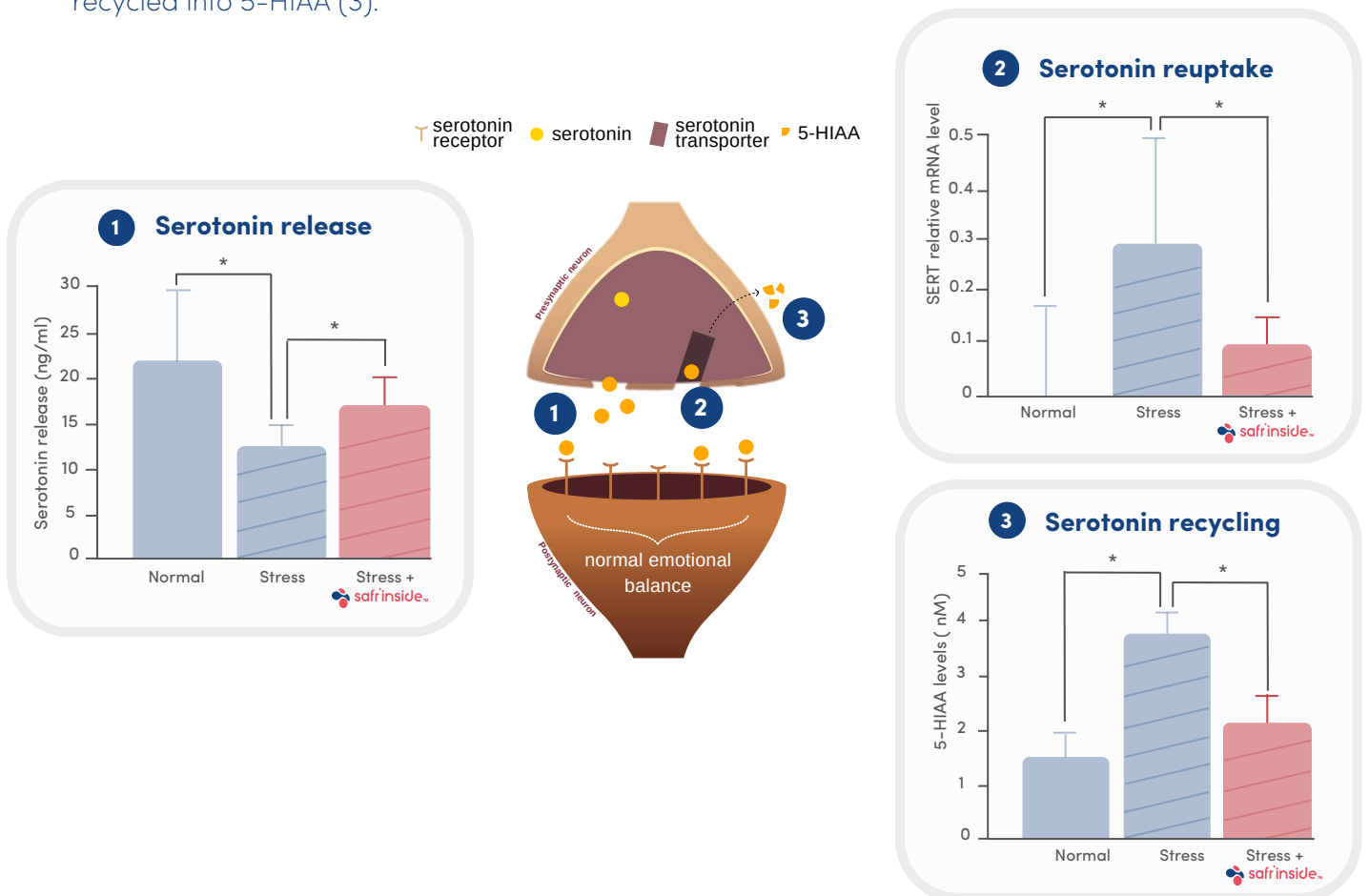
With 38 compounds identified, Activ'Inside has the highest saffron characterization. Among them, we guarantee that each batch contains the 25 compounds responsible for the improvement of emotional balance: Saframotivines.

# DEMONSTRATED MECHANISM OF ACTION ON SEROTONIN

The transmission of serotonin, also known as the « happiness neurotransmitter », is dysregulated during PMS. Safr'Inside™, due to the safranal (0,2% UHPLC) it contains, was investigated for its action on serotonin.



At the synaptic level, serotonin is released and transmitted to its receptor (1), enabling normal emotional balance. Serotonin transporter (SERT) recaptures serotonin (2) and prevents it from delivering its message, inducing a disturbed emotional balance. Following reuptake, serotonin is recycled into 5-HIAA (3).



Safr'Inside™ significantly restores serotonin transmission through the inhibition of serotonin reuptake & recycling. As serotonin is dysregulated in PMS leading to emotional imbalance, Safr'Inside™ appears as a solution to limit PMS symptoms.

# CONSUMER-APPROVED EFFECTIVENESS ON PMS SYMPTOMS

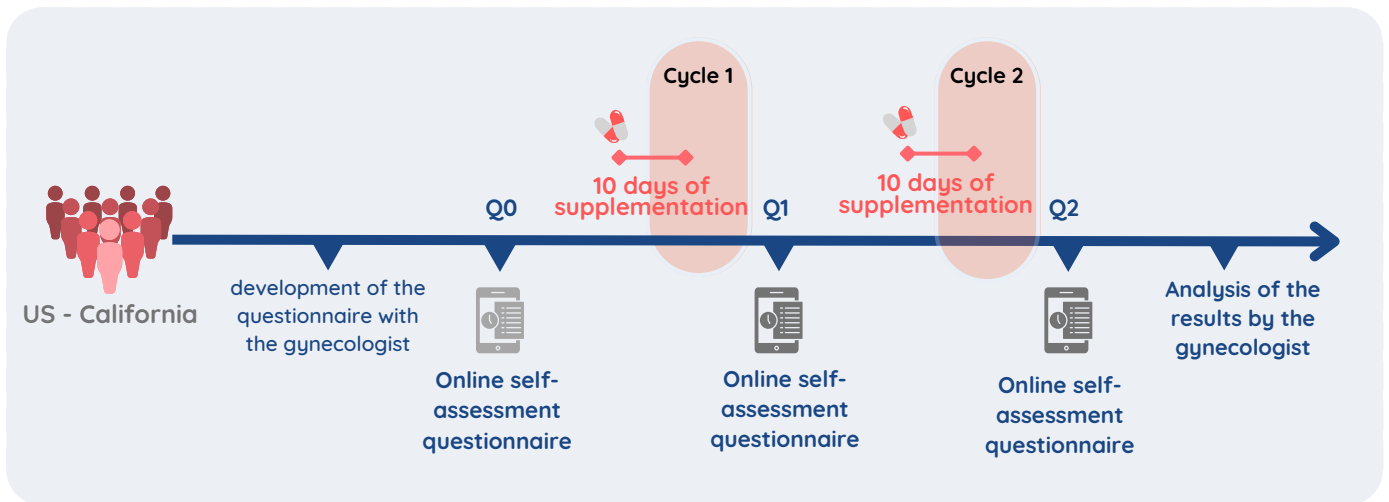
## OPEN STUDY UNDER MEDICAL SUPERVISION: DESIGN



The effectiveness of Safr'Inside™ on PMS was assessed in an open study under the control of a gynecologist, including a self-assessment questionnaire. Discomfort level of psychological and physical symptoms of PMS were assessed by participants before and after each cycle of supplementation.

 <b>40</b> HEALTHY	 ONCE DAILY <b>30MG</b> WOMEN	 2-CYCLE CURE	CONDUCTED IN: 
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Women were supplemented during 2 menstrual cycles with 30mg of Safr'Inside™ for 10 days, starting 5 days before the menstruation begins.



**Q0** : before the start of the program

**Q1** : after the first cycle of supplementation

**Q2** : after the second cycle of supplementation

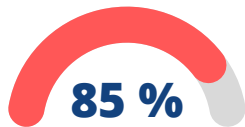
# CONSUMER-APPROVED EFFECTIVENESS ON PMS SYMPTOMS

## OPEN STUDY UNDER MEDICAL SUPERVISION RESULTS ON PSYCHOLOGICAL SYMPTOMS

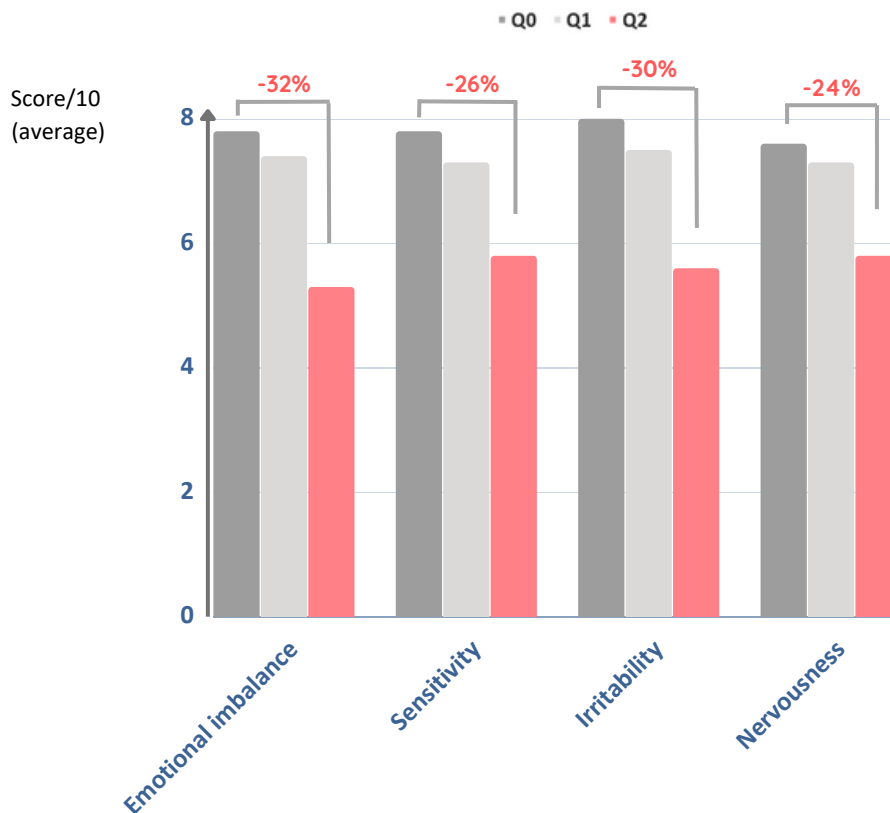
The supplementation with Safr'Inside™ allowed an improvement of several psychological symptoms associated with PMS: emotional imbalance, irritability, sensitivity and nervousness. These benefits were growing with time with a decrease of the discomfort throughout the supplementation.



- Have felt an improvement in emotional balance
- Have felt a decrease in irritability



- Have felt a decrease in sensitivity
- Have felt a decrease in nervousness



Thanks to its ability to restore serotonin transmission, Safr'Inside™ helps to decrease the discomfort linked to psychological symptoms in women suffering from PMS.

# CONSUMER-APPROVED EFFECTIVENESS ON PMS SYMPTOMS

## OPEN STUDY UNDER MEDICAL SUPERVISION: RESULTS ON PHYSICAL SYMPTOMS

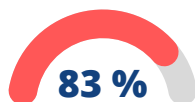
The supplementation with Safr'Inside™ allowed an improvement of several physical symptoms associated with PMS: menstrual discomfort, legs and stomach discomfort, water retention and physical fatigue. These benefits were growing with time with a decrease of the discomfort throughout the supplementation.



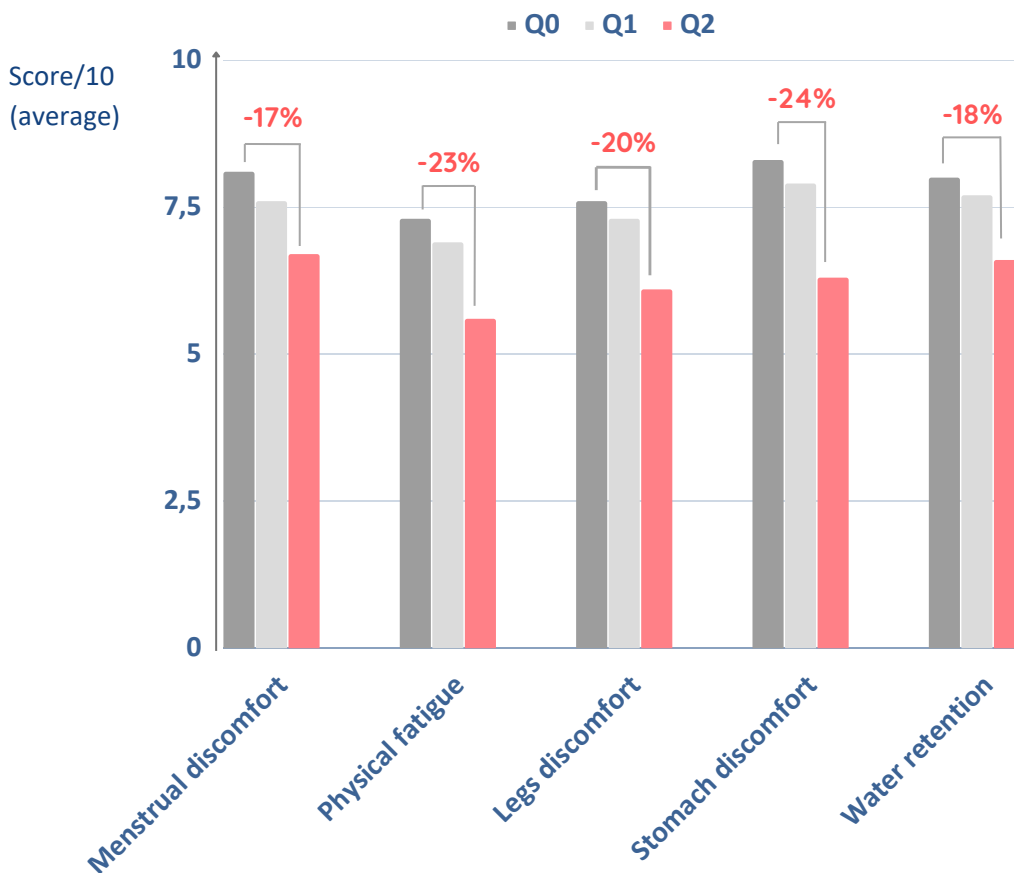
- Have felt a decrease in legs discomfort
- Have felt a decrease in stomach discomfort
- Have felt a decrease in water retention



- Have felt a decrease in physical fatigue



- Have felt a decrease in menstrual discomfort



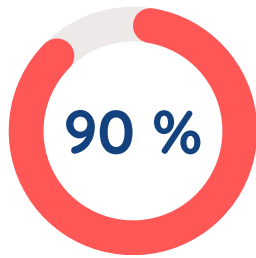
Safr'Inside™ helps to decrease the discomfort linked to physical symptoms in women suffering from PMS, thus confirming the traditional use of saffron.



# CONSUMER-APPROVED EFFECTIVENESS ON PMS SYMPTOMS

## OPEN STUDY UNDER MEDICAL SUPERVISION: SATISFACTION RESULTS & MEDICAL OPINION

After 1 cycle



women **satisfied**  
women declare that Safr'inside™ is **effective**  
women declare that Safr'inside™ **meets their expectations**  
women declare that Safr'inside™ **helps to feel fine during menstrual cycle**  
women declare that Safr'inside™ is **more effective than other competitors**  
women **recommend it**

After 2 cycles



**4** DAYS



On average for all women, improvements were perceived after 4 days of supplementation

**90%**



Of participants took **less painkillers** than during cycles without Safr'Inside™

The benefits of Safr'Inside™ were perceived by women on both physical and emotional symptoms associated with PMS. Moreover, these results were **quickly perceived, after 4 days** on average, achieving 90% satisfaction after the first cycle, rising to 100% after the second.

Based on these results and his medical experience, the gynecologist monitoring the study shared his opinion of the product:

"The psychological and physical symptoms associated with PMS are greatly improved"



"The open study shows that Safr'inside™ was fully satisfactory and provides a real solution to the frequent problem of premenstrual discomfort."

## WHY CHOOSING SAFR'INSIDE™?

Safr'Inside™, the full spectrum saffron extract with the richest concentration in safranal UHPLC, is a promising solution to relief emotional & physical symptoms occurring during PMS.

### Why Safr'Inside™?

- 1** Safr'inside™ helps 100% of women to feel good during menstrual cycle (open trial under medical supervision)
- 2** Proven mechanism of action on serotonin, known as the "happiness neurotransmitter" dysregulated during PMS (clinical ex vivo study)
- 3** The only patented encapsulated saffron extract with the highest safranal concentration (0,2% UHPLC)
- 4** CSR engagement
- 5** Made in France



Causal link between Safr'inside™ consumption and better emotional balance

Reduced stress

**Clinically tested**  
Consumer-approved effectiveness

**BETTER STRESS MANAGEMENT**  
Demonstrated mechanisms of action

**CLEAN LABEL**

**MADE IN FRANCE**  
Patented in several countries  
Protects neurons against stress-induced toxicity

**Only encapsulated saffron extract**  
Demonstrated action on serotonin, the "happiness hormone"

**EFFECTS ON PMS AFTER 4 DAYS ON AVERAGE**  
Proprietary encapsulation process  
Demonstrated bioavailability

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- Open trial under medical supervision, june 2023

### Want to know more?

Contact us to receive downloadable documents including Safr'Inside™ technical data sheets, product specifications and clinical trial results.

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