

Safr'Inside™: the
safranal-rich
saffron
extract that
highlighted
for the first time
under medical
supervision,
a connection
between its
consumers'
feedbacks
and
proprietary
clinical/
preclinical
studies

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For more than a year now, we have been faced to an uncountable number of articles regarding the dramatic increase in stress levels around the world. Various solutions are thus put forward to try to alleviate this growing problem. But wouldn't it be time to give consumers a voice? To understand how its premium ingredient could help improving the daily life of the populations in those troubled times, Activ'Inside decided to realize a life-sized study under medical supervision. Between March and April 2021, no less than 102 consumers with chronic or temporary stress volunteered to blindly test the benefits of a one-month supplementation with Safr'Inside™, the only encapsulated saffron extract that offers the highest concentration safranal, a saffron key metabolite known to improve mood. Indeed, after 2 proprietary at the beginning of the year validated the clinical effectiveness and demonstrated the mechanism of Safr'Inside™ through the action of its safranal content, it was now time to collect the opinions of the main people involved: consumers themselves. The purpose was twofold:

- 1 to support Activ'Inside's will to deliver effective ingredients to its clients so they can answer consumers' needs with their dietary supplements, and
- 2 to get consumers' feedbacks on our ingredients for continuous improvement.

For objectivity purposes, Activ'Inside has entirely entrusted the project to Expansion Consulteam, a reference agency in the field of open studies.

In addition, because science is the essence of Activ'Inside, this open study was realized under the supervision of a general practitioner with nutritionist and phytotherapist-aromatherapist degrees. She met the 102 participants both before and after the 30 days blind supplementation with 2x15mg of Safr'Inside™. She evaluated their daily stress intensity and the way they managed it using the well-recognized Perceived Stress Scale (PSS) questionnaire. In between, consumers gave their own feedback via 3 questionnaires administered at day 0, day 7 and day 30.

The tested population involved 52 women and 50 men with an average age of 41. Mental overload, pressure at work, family difficulties... the reasons for their stress could be numerous but they all felt that it was far too omnipresent in their daily lives. "It was really timely because I was at that time in a peak of unmanageable stress." Pascal, 45 years-old, explained to us.

An effectiveness validated by the consumers

After only 7 days of daily supplementation

with Safr'Inside™, first significant differences were reported both on daily stress and moral (Figure 1). Stress and moral respectively decreased and increased between days 0 and 7 and significantly continued to do so between days 7 and 30: the benefits of Safr'Inside™ on stress and moral were maintained throughout the month of supplementation and were even stronger and stronger.

The doctor did perceive those improvements among the 102 participants: "On the second interview, I immediately felt a difference. [...] they (editor's note: the consumers) were much calmer; you could feel them more appeased." Indeed, according to the validated questionnaire PSS and to the scoring guidelines, the average consumer score shifted from a "moderate" to a "low" stress level, with a 39% reduction in stress levels between the beginning and the end of the study. To be more specific, the anxiety and stress feelings were reduced by 60%, and irritability by 46%.

In addition, as stress and moral are cornerstones of health, consumers reported a significant improvement in their general health condition ($p < 0.0001$).

A quick solution: effects felt in less than 5 days

When it comes to stress, it is important to remember that consumers are generally looking for a solution effective quickly. After effectiveness, speed of action is the second most important reason for product loyalty¹. For 84% of participants, the first effects were quickly felt, with an average delay of about 4.7 days. Consumers sometimes even confided the health practitioner about the speed of effectiveness: "some mentioned two days, others did not say when, but we felt that it was quite fast. They didn't have to wait 30 days to feel an improvement.". And indeed, this speed pleased the participants, especially since half of them had already tested other stress solutions but without being convinced by their effects. To better understand the collected consumers feedbacks regarding their one-month supplementation with Safr'Inside™, Activ'Inside interviewed three of them, with different backgrounds but who used food supplements to relieve their stress in the past:

What do consumers say?

Pascal: "As soon as I took it [Safr'Inside™] I was impressed by the very fast results. [...] I saw the difference right away; besides I was in a stressful period at my job. After two days, I felt more zen, without being sleepy so it was really 100% beneficial!"

Anne: "In 48 hours I felt a real benefit, I was sad when the cure ended! [...] For someone who, like me, has just a lot of work and has to attend a lot of meetings, you feel much calmer very quickly,

you feel better. I can only attribute this to this food supplement (editor's note: Safr'Inside™). Nothing else in my life could have explained this!"

Sandrine: "Before the treatment I was stressed, anxious, tired and irritated. Throughout the course of the supplementation, I saw a really effective evolution. After one week I was already less stressed, less tired, more joyful and more positive."

Activ'Inside: "Compared to the products you have already tried to manage stress, what would you say about the effectiveness of Safr'Inside™?"

Sandrine: "When I take a supplement, I would like it to act immediately! It is not the case, it is long cures each time. What I expect from a new product is direct effectiveness. [...] Compared to the products I usually use, it [Safr'Inside™] was very effective."

Pascal: "I wanted something that was effective, and I never found it. [...] I did it [the open study under medical supervision] without really believing it. It's true that I had already taken a few things before, but what surprised me the most was that from the very first days I felt a radical difference."

Anne: "That's what I liked about the capsules: you really feel a difference, it's really noticeable. In two days, you feel a clear improvement! It is not the same thing with this supplement, and what usually is present on the market!"

Correlation between consumers' point of view and science observations

Thanks to its effectiveness, Safr'Inside™ convinced the consumers: at the end of the month, more than 8 out of 10 participants declared themselves satisfied with Safr'Inside™, and the same amount of people would recommend it to someone close to them (83%). In addition, 78% of participants declared that they would buy Safr'Inside™, and even tried to get information from health practitioner supervising the study to find out where to get it: "A good dozen of them asked me if I could tell them the name of this saffron extract that they had blind tested, and when it would be available or how they could get it so that they could use it again or even continue using it. And many of them told me that they had already used other plants in the past but that they had not had the same rapid effect as with Safr'Inside™ and that is why they were interested in taking it again."

Those results corroborate the ones from the clinical study published earlier this year (Jackson et al. 2021). Using a double-blind, randomized, parallel groups design involving 56 healthy individuals with non-pathological feelings of stress and/or anxiety and altered mood, Activ'Inside demonstrated the effectiveness of Safr'Inside™ to help manage a stressful situation and to restore their altered mood. Thanks to an innovative study conception, new piece of information about Safr'Inside™ mechanism of action were highlighted. Regarding stress management, the intake of 30mg of Safr'Inside™ led to the maintain of the Heart Rate Variability (HRV) index while it decreased in the placebo group. This indicator can be interpreted as the capacity of the organism to adapt to its environment: a reduced HRV indicates a more unresponsive system, with greater difficulty in coping with external stresses. The heart rate, and therefore the HRV, is controlled by the Autonomic Nervous System (ANS) which is organized into 2 branches: the sympathetic nervous system and the parasympathetic nervous system. If the first is intended to put the body on alert to face a stress,

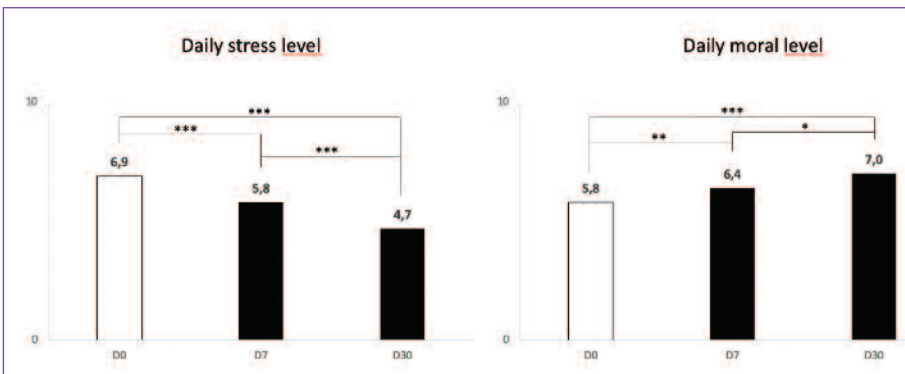


Figure 1: Consumers' daily stress and moral evolution throughout the open study under medical supervision testing a 1-month supplementation with Safr'Inside™. Levels are evaluated on Days 0, 7 and 30 using a 10-points scale. ***: $p < 0,0001$; **: $p = 0,0003$; *: $p = 0,0006$.

the second allows the body to rest. The HRV reflects the balance between these 2 systems. Because Safr'Inside™ did not influence some functions regulated by the sympathetic system, such as sweating, it can be concluded that relaxing effect experienced with Safr'Inside™ comes from the activation of the parasympathetic system rather than the inhibition of the sympathetic one. As explained by the health practitioner who supervised the open study, maintaining the balance between sympathetic and parasympathetic system by activating the latter is a key mechanism in stress management: "In the peripheral nervous system, the sympathetic/parasympathetic systems are involved in maintaining the physiological balance of the organism. In case of stress, the sympathetic system will be oversolicited and will push the organism to fight, while the parasympathetic system will fail. In order to fight stress and mental overload, we need to find a balance between these two systems". This demonstrated mechanism of action on the peripheral nervous system could thus explain why the participants supplemented with Safr'Inside™ did perceived a significant decrease in their daily stress.

But Jackson et al. 2021, brought also new pieces of evidences on a significant correlation between the assimilation of Safr'Inside™ by the body and the mood improvement (validated POMS-2 questionnaire). Indeed, when stress persists the body's adaptation resources become oversolicited and will run out. This will manifest itself in negative emotions such as anxiety, anguish, and mood alteration. Serotonin and dopamine, which are the mediators of good emotional balance, tend to be depleted especially during chronic stress. For a long time, saffron mechanism of action has been based on the strong hypothesis that its safranal and crocins content respectively inhibited serotonin and dopamine reuptake. This idea was especially supported by several clinical studies showing that saffron could be as effective as *Selective Serotonin Reuptake Inhibitors* class of antidepressants. To further understand saffron's mechanisms of action, and in particular Safr'Inside™'s, which has the highest concentration of this safranal on the market, Activ'Inside™ has worked with various academic partners. According to the first preclinical results using the validated Forced Swim Test (FST) published in Monchaux de Oliveira et al., 2021, a supplementa-

tion with Safr'Inside™ led to the following behavior improvements: decreased immobility time, increased swimming time and identical climbing time. This pattern is the one specific to a supplementation with *Selective Serotonin Reuptake Inhibitor* or even pure safranal (Figure 2). Both these results suggest that the benefits of Safr'Inside™ should be attributed to its high concentration in safranal, and that it is acting on serotonin transmission. To confirm this hypothesis, indicators related to serotonin transmission were analyzed. It appeared that Safr'Inside™ did influence serotonergic system by reducing by up to 50% the production of the transporters dedicated to the reuptake of serotonin, thanks to its safranal content.

But how could this saffron extract be that effective? In reality, the key success of Safr'Inside™ is the perfect combination of a thousand-year-old know-how and a state-of-the-art technique.

Sustainable sourcing valorized by a state-of-the-art technology

To manufacture the best extract, it is required to select the best raw material. This is why Activ'Inside decided to source its saffron in Iran where a unique expertise in its cultivation has been passed on from generation to generation for

thousands of years. Today, its quality is even recognized with an appellation of origin. Over there, the persistence of arid and semi-arid climate resulted in water scarcity and brought challenges regarding food security improvement and livelihood of local residents. Optimized used of the seldom water springs for the cultivation of a high added value product such as saffron created unique odds for farmers and residents to improve their living conditions, and create considerable jobs opportunities. In this region, rainfall usually does not exceed 250mm per year: there was thus a need rainwater harvest. 3,000 years ago, Iranian civilization created a unique and innovative system to transfer the water from the highlands to the crops in the plain: the Qanats. Still running and used by local communities, qanats are maintained by traditional systems. In 2014, the need to preserve this cultural heritage led it to be classified by the FAO as a Globally Important Agricultural Heritage System (GIAHS) while in 2016, 11 qanats got classified World Heritage Site by UNESCO. Indeed, still running and maintained by traditional systems, qanats bring water resources in a semi-arid region to maintain a local agriculture and contributes to the enrichment of the landscape biodiversity. The structure of a qanat is simple. It consists of a horizontal tunnel running through an

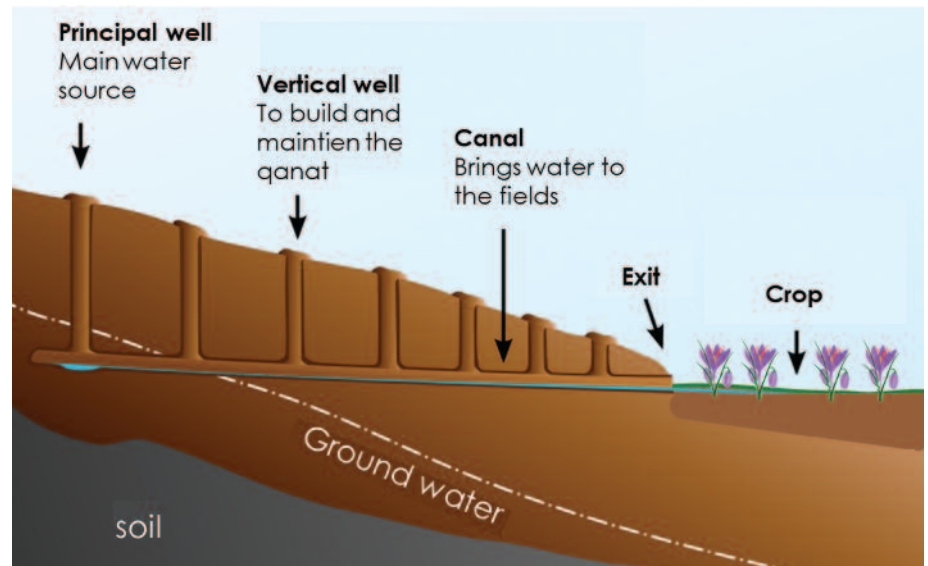


Figure 3: Simplified representation of a qanat construction, Adapted from 2018 GIAHS report

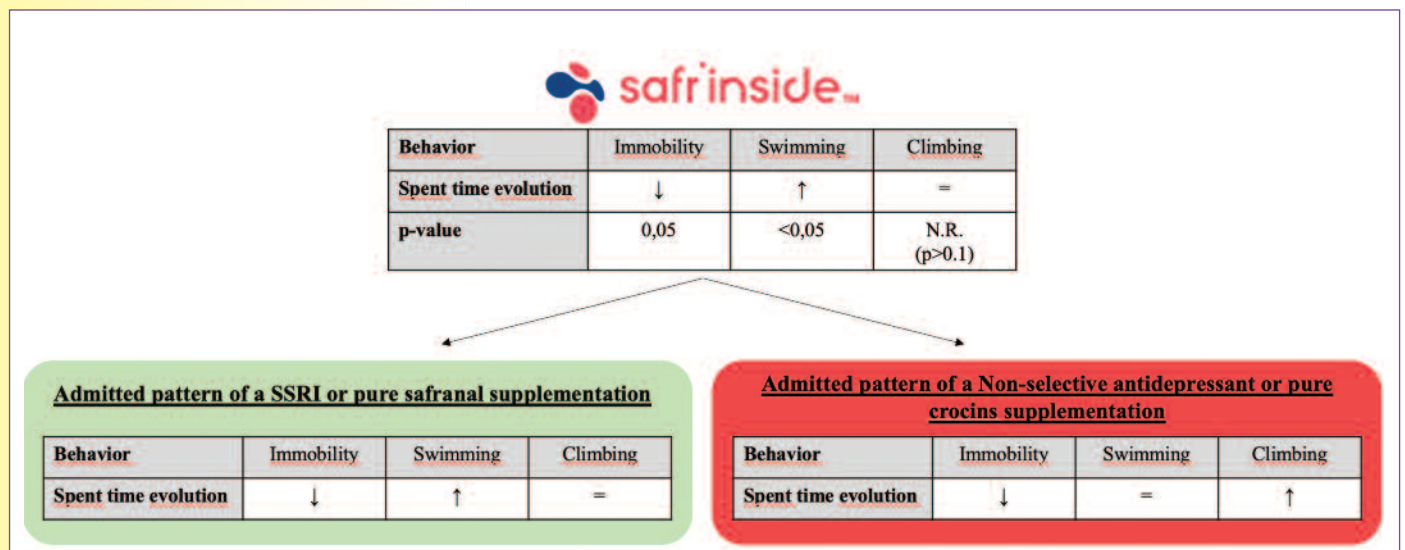


Figure 2: Comparison of the pattern of the evolution in mice behaviors during the Forced Swim Test following administration of Safr'Inside™ at 6,25 mg/kg (i.e. 30mg human equivalent dose), with the recognized ones following a supplementation with SSRI, pure safranal, non-selective antidepressant or pure crocins.



incline in which water flows by gravity after being collected in the mother well (Figure 3). Qanats allow the collection of water towards several crops, including the ones of *Crocus sativus* used to produce Safr'Inside™.

When the *Crocus sativus* blooms once a year, farmers pick flowers in the early morning. The female reproductive organs, the stigmas, are manually cut off and dried. Because the role of the stigma is to attract the insects, it is highly visible and fragrant, respectively thanks to its crocin and safranal. The most concentrated part is the very top of the stigma, named "Sargol" in Persian language. This is why Sargol is considered the top quality and is used to produce Safr'Inside™. The purity and grade of both raw material and extract are certified by 10 complementary adulteration tests conducted by independent laboratories to ensure the product's nobility.

Once the best raw material is selected, the extraction process must be adapted to the fragility of the saffron. Indeed, the top priority is to preserve the safranal: this volatile compound evaporates during the extraction process. Activ'Inside developed a specific patented extraction method to trap saffron compounds into the final extract and obtain the highest concentration in safranal. This is what we call "encapsulation". In addition, this soft process named "Tech'care™" preserves the raw material: Safr'Inside™ is the only saffron extract where up to 95% of saffron compounds identified by scientists are recovered.

From the sustainable sourcing of the raw material to the use of the best state-of-the-art technology, every step of the development process of Safr'Inside™ has been carefully optimized. This approach allowed to obtain the highest concentration of the saffron benefits, and to have a real positive impact on the daily life of 102 consumers, as witnessed by the health practitioner supervising them.

References:

1 Stress and Sleep OTC/Dietary supplements study by Expansion Consulteam, 2020



ProBiotix enters exclusive South Korean distribution deal for CholBiome®

Prominent life science developer, ProBiotix Health, has entered into an exclusive deal with Inscobee for the distribution of CholBiome® in the Asia Pacific region.

ProBiotix is a leading developer of scientifically backed probiotic products that improve cardiovascular health utilising the microbiome-liver axis, while Inscobee, a public company on the Korean stock market (KOSPI) with a group turnover valued at \$52.2m, is focused on expanding the bio-tech, nutraceutical and health supplement area of their business.

Over the past decade, there has been an increase in chronic diseases in Korea, with a notable rise in cardiovascular diseases (CVDs). CVDs have become one of the leading causes of morbidity and mortality in Korea and in fact are the second most common cause of mortality in the country.¹

Inscobee sells and promotes nutraceuticals through hospitals and a consumer distribution base through Korean off-line channels such as Holland & Barrett stores, hypermarkets, home-shopping, and e-commerce channels including on-line malls, open markets, influencer markets and live commerce markets.

Seung-Hyeon Nam, Director of Inscobee says

the company was very pleased to introduce CholBiome® products to the Korean healthcare market. "We believe CholBiome has great potential to fill the void of safe and beneficial cardiovascular health needs in the nation. We expect that it will play a big role as a flagship product of Inscobee's healthcare business and look forward to a long and successful partnership with ProBiotix Health."

Mikkel Hvid-Hansen, Commercial Director of ProBiotix Health, said the agreement is another milestone in a series of deals in the Asia market, which help build LPLDL® and CholBiome's reputation and brand awareness in the region. "Inscobee is the ideal partner in the fast moving, highly dynamic and competitive South Korean health food markets and gives us the ability to offer consumers innovative and effective natural solutions which stand out in the market.

"By entering deals for CholBiome® and LPLDL® in India, China, Malaysia, Singapore, Indonesia, Philippines, Taiwan, Australia, and New Zealand, ProBiotix is growing sales and developing a brand presence in these strategically important Asian growth markets," he concluded.

Reference:

1 <https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.119.310859>

Nestlé explores emerging technologies for cultured meat

To understand the potential of future meat alternatives, Nestlé is closely monitoring scientific trends and exploring emerging technologies. The company is evaluating innovative technologies to produce cultured meat or cultured-meat ingredients with several external partners and start-ups. Such novel technologies can lead to more environmentally friendly products.

For example, scientists at Nestlé Research in Lausanne are working with Future Meat Technologies, a leading cultured-meat start-up, to explore the potential of cultured-meat components that do not compromise on taste or sustainability. Future Meat Technologies' novel and cost-efficient proprietary technology can produce non-GMO cultured-meat components from animal cells, therefore reducing the need for land and resources to raise animals.

Reinhard Behringer, Head of the Nestlé Institute of Material Sciences at Nestlé Research says: "For many years we have been investing in our protein expertise and the development of proprietary technologies for plant-based meat alternatives, allowing us to continuously expand our wide range of tasty and nutritious products with a lower environmental impact. To complement these efforts, we're also exploring technologies that could lead to animal-friendly alternatives that are nutritious, sustainable, and close to meat in terms



of taste, flavor, and texture. We are excited to understand their potential."

People are increasingly reducing or eliminating animal products from their diet for many reasons including animal welfare, health and wellness as well as environmental concerns. This has led to the rapid growth of plant-based meat and dairy alternatives. Providing people with delicious, nutritious, and sustainable plant-based products is a priority for Nestlé. Today, the company offers a wide range of meat and dairy alternatives that are suitable for flexitarians, vegans, vegetarians, as well as people with special dietary needs.

By exploring breakthrough technologies, Nestlé is showing a strong innovation drive and openness towards novel concepts. This will help the company to continuously transform its portfolio with products that are good for people and the planet.