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Design of an Effective Nutraceutical ("SR45") for Low Mood Management

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Abstract: Introduction: Herbal products play a crucial role in traditional Chinese medicine, offering a holistic approach to disease treatment. Botanicals and their active components have shown promise in addressing depression-like symptoms. Unlike antidepressant medications, botanicals offer a natural alternative with milder side effects. This study explores the potential of botanical compounds as antidepressants. Natural Products for Low Mood Management: Crocus Sativus (Saffron): Derived from the Crocus sativus flower, saffron has demonstrated effectiveness in relieving symptoms of mild to moderate anxiety, comparable to standard antidepressants. Cost-effective petal extracts have proven to be viable alternatives. Rhodiola Rosea (Rhodiola): Used traditionally to enhance physical and mental performance, Rhodiola extracts have shown promise in reducing anxiety and depression symptoms. Development of SR45: Bioactive compounds hold significant potential for enhancing nutraceutical functionality. Encapsulation systems have emerged as a transformative technology for improving bioactive stability and bioavailability. SR45, developed with Rhodiola on a lipid basis and advanced encapsulation techniques, aims to enhance the bioavailability of key bioactive ingredients. Preliminary Clinical Results Obtained with SR45: A randomized clinical trial evaluated SR45's efficacy and safety in individuals with low mood. Participants taking SR45 experienced a statistically significant reduction in depression and anxiety symptoms compared to the placebo group. Both groups showed improvement, highlighting the placebo effect, essential for robust study execution. No adverse events related to SR45 were observed, indicating its safety. Conclusions: Daily consumption of SR45 capsules over 8 weeks led to a reduction in depression in individuals with mild symptoms. SR45 also demonstrated effectiveness in reducing anxiety in individuals with mild to moderate symptoms. SR45 was found to be safe for consumption at the specified doses over the 8-week period. This preliminary study suggests that SR45 holds promise as a natural supplement for managing low mood. Further research is warranted to validate these findings and explore the potential of SR45 in a larger population.

Keywords: Crocus Sativus, Rhodiola Rosea, Low Mood

1. Introduction

Herbal products are the main component of traditional Chinese medicine, which embodies the intact theory for treating diseases [1]. Botanicals or their active components have been extensively investigated in the treatment of depression-like behaviors and, specially, the mixed use of botanicals has a previous role in improving the symptoms of depression [2].

Antidepressant medications have strong side effects and safety concerns, and withdrawal can be very difficult. Interestingly, some botanicals and active ingredients have the effect of regulating neurotransmitters. As we all know, the active or botanical components are formed naturally and the toxicity or side effects are relatively mild. Therefore, the active components have the potential to become antidepressants [3].

2. Natural Products for Low Mood Management

2.1. Crocus Sativus (Saffron)

Derived from the stigma of the Crocus sativus flower, saffron is commonly used as a spice and medicine in the Middle East and South Asia. In patients with mild to

moderate anxiety, saffron extracts have been reported to be effective in relieving symptoms in several studies. Studies also show that the effects are comparable to standard antidepressant drugs. In addition, less expensive petal extracts have also been tested and found to be effective substitutes [4].

2.2. Rhodiola Rosea (Rhodiola)

Rhodiola (Rhodiola rosea) is a perennial plant used in traditional medicine in Asia and Eastern Europe to improve physical stamina and mental performance. Results from studies of the root extract in patients with anxiety and depression show that it can reduce symptoms compared to placebo. In adults with stress-related fatigue, an extract of R. rosea was no better than placebo in reducing depression scores [5].

3. Development of SR45

Many bioactive compounds are a good choice that can be used to enhance nutraceutical functionality. However, due to the low stability and bioavailability of many bioactives (both hydrophobic and hydrophilic) within the heterogeneous structure of food supplements and in the gastrointestinal tract, it becomes extremely difficult to convey real health benefits to consumers [6].

Recent developments in the application of encapsulation systems for nutraceutical development are proving to be a game changer that has raised the expectations of researchers, manufacturers, and consumers regarding the possibility of enhancing the functionality of bioactives within food supplements. In this direction, new administration systems have been manufactured to stabilize and improve the biological activity of bioactive compounds [7].

For these reasons, the SR45 designers have worked in two ways:

1) The use of Rhodiola on a lipid basis.

2) New encapsulation techniques for bioactive ingredients.

Rhodiola rosea (Crassulaceae) roots have been used in traditional and modern medicine for the treatment of different diseases and in recent years, root extracts are applied as nutraceutical ingredients offered worldwide. The main factors that limit the oral bioavailability of hydrophobic bioactive agents are known: bioaccessibility, absorption and transformation, and how oils can control these processes and improve bioavailability, which facilitates the design of new formulations to improve the bioavailability of nutraceutical products by increasing bioavailability of specific bioactives [8]. Phytochemical research on Rhodiola has focused mainly on salidroside, rosin, rosavin and rosarin although there are other important components of R. rosea such as flavonoids, tannins, gallic acid and its esters and essential oils that are have described in detail only when Rhodiola is offered as an oil, and for this reason SR45 researchers developed a Rhodiola oil extract that would contain and preserve all of the bioactive ingredients of this botanical [9].

In addition, assuming that the chemical composition of Rhodiola is determined genetically, the SR45 researchers selected the species of the genus Rhodiola rosea with a specific chemotype, avoiding other Rhodiola species that have a different phytochemical and bioactive composition [10].

Regarding the administration systems where the bioactive ingredients are included, the usual matrices (capsules, tablets, sachets.) have not been fully explored for the administration of botanical bioactives despite the fact that it is known that they can greatly influence the metabolism and bioavailability of bioactive ingredients [11]. That is why the SR45 researchers decided to include the active ingredients of saffron and Rhodiola in a new delivery system in order to obtain objective data on clinical efficacy and safety compared to traditional gelatin capsules. The initial advantages of the system are that it increases the effectiveness of the formula, increases the bioavailability of the active compounds through a prolonged sequential release and that it is 100% vegetable.

The oral bioavailability of a nutraceutical can be limited by various physicochemical and physiological phenomena: release from food matrices, solubility in gastrointestinal fluids, interaction with gastrointestinal components, chemical degradation or metabolism, and epithelial cell permeability. Therefore, nutraceutical bioavailability can be improved by designing food matrices that control their bioaccessibility, absorption, and transformation within the gastrointestinal tract [12]. The oral bioavailability of many lipophilic bioactives, such as nutraceuticals, is known to be relatively low due to their low solubility, permeability, and/or chemical stability within the human gastrointestinal tract, and the oral bioavailability of lipophilic bioactives can be improved by design of food matrices that control their release, solubilization, transport and absorption within the intestine [13]. Accordingly, the new delivery systems can be used to improve the oral bioavailability of lipophilic bioactives and, therefore, the efficacy linked to less variability in biological effects [14].

Thus, SR45 is a nutraceutical encapsulated with a modern technology that contains 300 mg of dry extract of Rhodiola rosea root (>5.0% of total Rosavins and >2.0% of Salidroside, measured by HPLC) and 70 mg of dry extract of stigmas of Crocus sativa L. (4.0% Safranal and 10.0% Crocins, measured by HPLC).

4. Preliminary Clinical Results Obtained with SR45

Over the years, several reviews [9, 15-17] and an observational study [18] suggest that the combination of Rhodiola and saffron could be useful for the treatment of mild-moderate depression and improve depressive and anxiety symptoms, highlighting the need to carry out other clinical studies that would contribute with more and better scientific solvency.

A study was conducted to measure the efficacy and safety of the use of SR45 through a randomized clinical trial to evaluate the efficacy of an extract of saffron and Rhodiola on subjects

with low mood. The intervention study in humans was approved by the ethical committee of the Catholic University of Murcia (UCAM).

The clinical trial was randomized, placebo-controlled, double-blind, with two groups depending on the product under study (placebo or saffron extract), in subjects with low mood who consumed 1 capsule of SR45 per day for 8 weeks.

A total of 117 subjects were included, of whom 107 completed the study. These subjects had low mood with a Hamilton Anxiety Scale score greater than 6 or a Hamilton Depression Scale score greater than 6 and complying with the following criteria:

1) Age equal to or greater than 18 years.
2) Subjects without psychological treatment or with psychological treatment of more than 4 weeks duration, or without psychopharmacological treatment or with psychopharmacological treatment with constant dose of antidepressants during the last 4 weeks, or with a combined treatment in which the psychological treatment has been started 4 weeks before the patient's inclusion in the study and the pharmacologist has had a constant dose of antidepressants for the past 4 weeks.
3) Subjects who are not taking food supplements or who are taking it during the last 4 weeks.
4) Subjects status regarding treatment (treatment yes or no) will remain the same throughout the study.

The products used in the study were:

1) SR45, daily dose 1 capsule, orally containing extracts of saffron and Rhodiola.
2) Placebo product, daily dose 1 capsule, orally containing Maltodextrin + Microcrystalline Cellulose.

Investigators included participants who met all protocol selection criteria. Only those participants who met all the inclusion criteria and none of the exclusion criteria were offered to participate in the study, providing them with detailed information about the procedures and tests they had to perform if they gave their consent to participate in it. In addition, the research team answered all the questions that the participant asked regarding their participation in the study.

The efficacy of the product under investigation was analyzed after comparing the differences between the groups (experimental and placebo) with respect to the evolution of the main study variable: measurement of depression and anxiety mood using the evaluation scale for depression of Hamilton Depression Rating Scale (HDRS) [19] and the Hamilton Anxiety Rating Scale (HARS) [20].

The safety of investigational products (IP) was assessed by recording Adverse Events (AEs) throughout the study, from the baseline visit to the final visit. In addition, all the signs and symptoms corresponding to side effects related or not to the PI were collected after prior communication from the participant, spontaneously or by indication of the research team, and were described in the corresponding form to document tolerability to it. These forms are documented in the investigator's data collection notebook (CRD) and were recorded during study visits.

The mean age of the volunteers taking SR45 was 27.79 ± 8.61 years and the mean age for the placebo group was 26.97 ± 8.87 years. There are no significant differences between these means, nor are there any between the means of body weight, height and body mass index (BMI) of both groups under study. Therefore, it can be concluded that the groups were homogeneous before taking the treatment.

The study included 51 men (25 in the SR45 group and 26 in the placebo group) and 66 women (33 per treatment group). Therefore, the population studied was also homogeneous in terms of gender.

The volunteers in this study had baseline depression values of 13.56 ± 5.05 and 11.75 ± 4.30 for the group that took SR45 and for the placebo group, respectively. These values, which correspond to mild depression, do not differ significantly from each other, so it is concluded that at the beginning of the study the groups were homogeneous in terms of the depression variable.

The volunteers began taking the assigned product (SR45 or placebo) daily and were scheduled to visit the research center twice during the 8 weeks of treatment to be measured on the Hamilton depression and anxiety scales. The visits were made on days 28 and 56.

When studying the variation of the depression variable throughout the study, a decrease in its values can be seen in the SR45 group, so that the reduction in depression over time is statistically significant ($p<0.05$) and the individuals taking SR45 reduced their depression at the end of the study by 4.79 ± 3.68 points, representing a difference between the final and baseline visits of 8.77 points, whereas individuals in the placebo group reduced their depression less, at 6.51 ± 4.82 points, which represents a difference between the final visit and the baseline visit of 5.24 points. The fact that the placebo group also experienced a significant reduction in depression supports the correct execution of the study, since the "placebo effect" that occurs in studies carried out on mood is clearly manifested. Thus, it is observed how individuals respond to placebo, improving the symptoms of depression, just for the mere fact of knowing that they may be receiving treatment and also being subjected to monitoring and care as part of the clinical trial protocol. This instills in the volunteer expectations of improvement, enthusiasm and a positive vision. Therefore, if the placebo group did not show changes, the correct execution of the study would have to be questioned.

When comparing the treatment groups throughout the 8 weeks of the study, it was found that depression in the group treated with SR45 was reduced in a statistically significant way ($p<0.05$) compared to the placebo group. Therefore, individuals improve their depression due to the consumption of SR45.

Regarding anxiety, at the baseline visit there were no significant differences between the two study groups (12.00 ± 5.22 and 10.96 ± 4.15 for the SR45 group and the placebo group, respectively), which means that both groups were homogeneous regarding the anxiety variable and, therefore, the final results are not influenced by differences in the starting population. The initial anxiety ranges correspond to mild-moderate anxiety levels. Both the subjects taking SR45

and those taking the placebo reduced their anxiety throughout the study in a statistically significant way ($p<0.05$). However, this reduction was greater in the group treated with SR45 which, starting from 12.00 ± 5.22 anxiety points, dropped it to 4.56 ± 4.04 points at the end of the study, which implies a difference of 7.44 points on the anxiety scale. The placebo-treated group showed a lesser reduction in anxiety at the final visit, 5.33 points, compared to the baseline visit. The importance of the presence of the "placebo effect" is once again emphasized, essential to ensure the correct execution of studies related to mood. When comparing the treatment groups throughout the 8 weeks of the study, it was found that anxiety in the group treated with SR45 was reduced in a statistically significant way ($p<0.05$) compared to the placebo group. Therefore, the individuals improved their anxiety due to the consumption of SR45.

There were no adverse events related to the investigational products throughout the study. Therefore, it can be said that both the intake of SR45 and placebo, at the doses indicated in the study protocol and consumed for 8 weeks, were safe.

5. Conclusions

1) Consumption of one SR45 capsule daily for 8 weeks reduced depression in individuals with mild depression.
2) The consumption of one capsule of SR45 daily for 8 weeks reduced anxiety in individuals with mild-moderate anxiety.
3) The consumption of one capsule of SR45 daily for 8 weeks was safe.

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