

An open prospective pilot study of a herbal combination “Relief” as a supportive dietetic measure during alcohol withdrawal

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Abstract

OBJECTIVE: A herbal combination (saffron extract, passion flower herb extract, cocoa seed extract, radish extract and black cumin extract) called “Relief” was designed as a supportive therapy of alcohol withdrawal syndrome (AWS). This combination was based on the scientific evidence of each constituent effect on AWS-like symptoms. In addition, our preclinical studies have shown the effectiveness of Relief on AWS detoxification. The rationale of the study was to document whether the oral intake of the designed content of Relief could have a positive effect on the course of alcohol detoxification by reducing some of the AWS in hospitalized patients. **METHODS:** This pilot study was performed as non-interventional, open, single-armed, prospective on 32 hospitalized patients entered for detoxification of alcohol withdrawal syndrome. Each patient received daily three capsules of Relief for 15 days, and AWS parameters were monitored, in addition to serum liver enzymes and quality of life which was evaluated using the Befindlichkeits-Skala (Bf-SR) scaling system. **RESULTS:** Relief administration significantly reduced the percentage of patients with hyperhidrosis ($r=0.815$, $p<0.001$), reduced serum liver enzymes by ~50–80% ($p<0.05$), and increased normalization of appetite ($r=0.777$, $p<0.001$). Besides, before the treatment began the Bf-SR scale was 28.3 ± 4.3 , which was typical for neurological syndromes such as depression or insomnia, and during Relief administration the Bf-SR scale significantly dropped to 15.6 ± 2.4 ($p<0.001$). As for the safety, four, but not serious, adverse events were observed; two of them may be product related. Finally, 84.4% of patients’ assessed Relief treatment as good to excellent and 87.5% of the patients declared an interest in reusing Relief for the next detoxification period. **CONCLUSIONS:** Despite the limitations of the present study, the findings showed the potential of Relief for the improvement of the clinical situation of patients with symptoms of alcohol withdrawal and therefore, justify a full-scale well-controlled study design to be implemented.

INTRODUCTION

Alcohol consumption is associated with a risk of developing health problems such as liver cirrhosis, cancers, injuries, and alcohol dependence (AD) (Baan *et al.* 2007; Shield *et al.* 2013). The highest alcohol consumption is present in the developed world mainly in Europe and the America's, and to lesser levels in the developing countries (WHO 2014). According to WHO global report, individuals above 15 years of age drink on average 6.2 liters of pure alcohol per year. These values are higher in Europe and the Americas, 10.9 L/year and 8.9 L/year, respectively (WHO 2014). The latter explains the occurrence of AD in 2.3% of the world population; 4% of the Europe population, 3% of the America's population and fewer percentages in the rest of the world.

AD is a dominant universal and a serious encountered condition that occurs following chronic alcohol consumption. AD is a physical dependence in which the body adapts to a particular effect and eliciting alcohol-specific physical or physiologic symptoms if alcohol is abruptly ceased (Sachdeva *et al.* 2015). These alcohol withdrawal symptoms termed alcohol withdrawal syndrome (AWS), range from mild to moderate such as sweating, nausea, headache, depression, anxiety, and insomnia. However, serious AWS can also occur such as visual hallucination, seizure and delirium tremens. Delirium tremens is a condition characterized by confusion, rapid heartbeat, and fever that may sometimes lead to death. These AWS comprise instabilities in a neurotransmitter circuits of the nervous system that are due to alcohol-related pathway (Koob & Nestler 1997; Hall & Zador 1997; DeWitte *et al.* 2003; Sachdeva *et al.* 2015). Therefore, management and pharmacological interventions to re-adjust the fluctuations in the neurotransmitter circuits and treat AWS are necessary. Medications with an effect against craving for alcohol are applied in therapy, but Cochrane reviews were inconclusive in regards to effectiveness and safety of pharmacological interventions in the treatment of AWS (Amato *et al.* 2011; Liu & Wang 2017). Therefore, a supportive therapy is essential and herbal supplements might have the favorable effects and could become a necessary asset in combatting addiction by increasing well-being.

The herbal combination "Relief" (saffron extract, passion flower herb extract, cocoa seed extract, radish extract and black cumin extract) is a food supplement designed for the improvement of well-being and the support of digestive functions (Qadan 2014; 2015; 2017). Due to the known properties of each herbal constituents on the equilibrium of the mood and the liver function, it was hypothesized that the use of the combination might have positive effects as a dietetic support of alcohol withdrawal (Qadan 2014; 2015; 2017). Specifically, saffron and passion flower herb were selected because of their positive impact on rest-

lessness, sleep disorders, anxiety and mood swings, which are typical symptoms during detoxification (Miyasaka *et al.* 2007; Sarris *et al.* 2013; Lopresti & Drummond 2014; Khazdair *et al.* 2015; Moshiri *et al.* 2015). Cocoa supports the cardiovascular system and cerebral blood flow and has been found to reduce blood pressure, and to be a central nervous system stimulant, cardiac stimulant, coronary dilatory, and diuretic actions (Ibero-Baraibar *et al.* 2016; Borghi & Cicero 2017), whereas radish and black cumin are known to support liver functions (Al-Jenoobi *et al.* 2010; Evans *et al.* 2014). Therefore, we have suggested that combining the individual effects of each herb should reduce some of the physical and psychologic AWS during alcohol detoxification, such as tiredness, anxiety, mood swing, palpitations, increased blood pressure, and impaired liver function.

The rationale of the study was to document whether the oral intake of the designed content of Relief could have a positive effect on the course of alcohol detoxification by reducing some of the AWS in hospitalized patients. The objectives of the present study were: 1) to document the effects of a 15-day oral intake of herbal extract mixture Relief on patients who have typical AWS; 2) to document data on the safety of application; 3) to establish power calculations required for a full-scale well-controlled study design; and 4) to evaluate logistic feasibility of a full-scale study, including issues of data collection, protocol adherence, and questionnaire design.

METHODS

Study design and location

This pilot study was designed to yield pharmacological and safety information when using Relief on patients that were hospitalized for having episodes of alcohol withdrawal. Therefore the study was performed as non-interventional, open, single-armed, prospective data documentation of dietetic effects of Relief during alcohol withdrawal. Furthermore, the study was conducted at the kbo-Isar-Amper hospital at Haar (Hospital Munich-East); a hospital specialized on in-patient alcohol withdrawal treatments.

Study approval

The test product Relief was registered under No. 101.11101.0.04428(2014 at the German Federal Institute for Consumer Protection and Food Safety (BVL, Bundesinstitut für Verbraucherschutz und Lebensmittelsicherheit). Following the product registration, a study protocol was submitted and approved by an independent ethics committee (Freiburger Ethik-Kommission International) on March 10, 2014. Also, the protocol included patient's insurance with HDI Gerling, insurance No. 85291545 03010 390 7296031 and the data documentation were made per the ethical principles defined by the Declaration of Helsinki.

Before study initiation, each subject has read and signed an informed consent for enrollment in the study following a detailed pre-prepared information material on the modalities of Relief composition, safety and use has been given.

Selection of study subjects

Subjects for this study were selected according to inclusion/exclusion criteria, and each subject had to fulfill the inclusion criteria, and not to violate the exclusion criteria as follows:

Inclusion criteria:

1. Subjects of either gender male or female age 18 years and above
2. Subjects who fulfill alcohol dependence only
3. Willingness to give written informed consent to the prospective collection and analysis of the data

Exclusion criteria:

1. Subjects with extreme cases of alcohol addiction (to be judged by the physician)
2. Subjects with polytoxicomania
3. Subjects with hypersensitivity to any of the constituents of "Relief"
4. Female subjects who are pregnant

The justification of pure alcohol dependence was made to have a proper evaluation of the findings. In addition, subjects selected should not have a severe case of addiction because the effects of a herbal preparation are unlikely to be observable in severe cases.

Sample size

This study was an exploratory pilot study, and the original plan was to include 60 evaluable subjects. However, due to slow recruitment, the study was prematurely terminated after the documentation of 34 patients. A primary reason for slow recruitment was the exclusion of severe and non-polytoxicomaniac cases. Such cases tend to accumulate around Christmas and Easter when many patients enter the hospital, but only very few were eligible for this study. Furthermore, exclusion of subjects patients was foreseen in cases where a violation of the in- or exclusion criteria was found. Two patients had to be excluded from the evaluation because of missing signatures for informed consent. Due to the strict handling of inclusion criteria no other included patient had to be retrospectively excluded.

Treatment capsule constituents, dosage and study duration

All extracts were purchased with certificates of analysis demonstrating reproducible and defined quality. Capsule manufacturing was made at the contract manufacturer Capsumed, specialized in capsule manufacturing. Each single capsule of "Relief" contains: 90 mg of cocoa seed extract (*Theobroma cacao*, semen, 45% of polyphenols); 30 mg of passion flower herb extract (*Passi-*

flora incarnata, herba); 15 mg of saffron extract (*Crocus sativus*, stigma, min. 2% of safranal); 165 mg of radish extract (*Raphanus sativus* var. *niger*, roots); and 100 mg of black cumin extract (*Nigella sativa* L., seeds) with no excipients were added.

As for the dose and schedule of dosing, each subject has been given one single capsule orally, three times a day for 15 days. The dose was selected according to previous clinical experience with each herbal constituents and corresponds to levels that used with typical foods and food supplements. Toxic effects were not expected with the selected doses. The investigating physicians were responsible for handing over the preparation to the patient.

Data quality assurance and variables assessment

All data were documented in a case report form (CRF), identified by patient number and initials and then were transferred to a computer-based database in tabulated form. A regular monitoring was made to discuss the progress of the study and to ensure that the data is correctly entered into the CRFs. During the study period, the study monitor had no access to personal data allowing the identification of a specific patient. Patient files with the original documentation are kept by the physician and archived according to the standing rules of medical practice. The CRFs are archived by the principal investigator for the duration defined for clinical research by corresponding EU regulations.

The variables were assessed based on verbal rating scale whereas the quality of life was evaluated using the Befindlichkeit-Skala (Bf-SR) scaling system (Zerssen & Petermann 2011). The Bf-SR is a diagnostic tool for the detection of mood since its first publication. In this study, we used the revised version where the procedure was slightly shortened, reviewed regarding language, and re-standardized on a population-representative sample. Furthermore, serum liver enzymes, GGT, AST and ALT, were performed and documented.

Statistical analysis

Data from the CRFs were assessed descriptively (means, standard deviations, minima, maxima, etc. of metric data; absolute and relative frequencies for categorical data). Missing data were replaced by the "Last Observation Carried Forward" method. Furthermore, one sample two-tailed student-t-test was applied to evaluate the effectiveness of "Relief" on quality of life Bf-SR scale raw data as well as on the transformed data based on population rank, T-value or Stanine. To assess changes in serum liver enzymes, paired 2-tailed student t-test was performed. In addition, a linear regression model was also applied to the assessed independent variables (percentage of subjects having the condition) that could be affected by treatment over time. The correlation coefficient (r) was analyzed on each operational variable with its scatter plot drawn.

RESULTS

Sociodemographic characteristics and anamnesis

The sociodemographic characteristics of the subjects enrolled in the study are presented in Table 1. Of the 32 subjects enrolled in the study, 65.6% were males, and 34.4% were females, 56.3% were divorced, and 59.4% were not employed.

Most of the subjects enrolled in the study have chronic cases of alcohol abuse; with a mean of 146.1 ± 121.1 months (range 6 to 504 months; median 120 months) since their first presentation of alcohol abuse. Twenty-five patients (78.1%) have previously gone through alcohol detoxifications, whereas in seven cases (21.9%) the current treatment was the first detoxification approach. Patients with previous detoxifications mostly had a long history of alcohol abuse, with an average of 10.4 ± 11.2 rehabs (min. 1, max. 50; median 6.0). The previous detoxification was completed by 21 of the 25 cases (84.0%). Only 3 (9.4%) subjects declared further physiological addictions, whereas 21 (65.6%) patients had informed about concomitant diseases and 19 (59.4%) patients took concomitant medication.

Monitoring of AWS

The assessment of hyperhidrosis was made on a three-point verbal rating scale (none, moderate, severe). Before initiation of treatment, hyperhidrosis was severe in 14% and moderate in 64% of the cases. During Relief administration the percent of patients with hyperhidrosis was reduced (Figure 1). This percent reduction was significantly correlated with the 15-day treatment ($r=0.815$, $p<0.001$) and was even higher during the first 6 days of treatment ($r=0.965$, $p<0.001$) because the percent of patients with hyperhidrosis did not change after that.

The assessment of percent appetite change was made on a three-point verbal rating scale: normal, low or high appetite. As expected, chronic alcoholism reduced

appetite in 44% of patients. During the 15-day treatment with “Relief”, subjects’ appetite showed a positive development towards normalization. The percent of patients with normal appetite significantly increased with treatment ($r=0.777$, $p<0.001$) (Figure 2).

During the study period, headache, anxiety, consciousness, and mood were also monitored. For unconsciousness, it was evident in 10% of the cases which was resolved after day 3 of treatment. Similarly, 20% of subjects had a headache and this percentage dropped to 10% on day 4 and remained as such till day 15 (end of study). As for anxiety, the percent anxious subjects before the study was above 30%; one case was severe, and then dropped to ~10% after the first day of treatment and the severe case became mild. Lastly, depressed mood was initially present in 45% of the cases and this percent significantly dropped during days 5 to 7 of treatment. However, the percentage of patients with depressed mood returned to be insignificant from the starting point of the treatment (Figure 3).

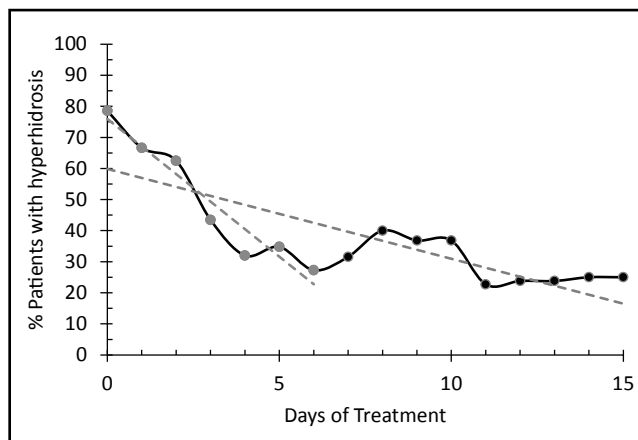


Fig. 1. The % patients with hyperhidrosis over days of treatment with Relief. A significant correlation with a 15-day treatment was observed (dotted line; $r=0.815$, $p<0.001$) and it was even higher during the first 6 days of treatment (dashed line; $r=0.965$, $p<0.001$).

Tab. 1. The sociodemographic data of the subjects enrolled in the study.

Parameter	Value/Percentage (n=32)
Sex	Male = 21 (65.6%) Females = 11 (34.4%)
Age	Average = 45.4 ± 10.5 yrs Range: 26–63 yrs Median = 47.5 yrs
Height	Average = 172.9 ± 8.9 cm Range: 157–193 cm Median = 175 cm
Marital Status	Single = 8 (25%) Married = 6 (18.8%) Divorced = 18 (56.3%)
Employment	Employed = 11 (34.4%) Part-time Employed = 2 (6.3%) Not Employed = 19 (59.4%)

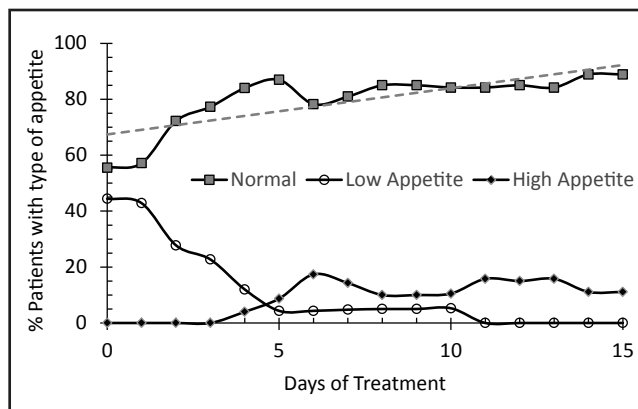


Fig. 2. The % patients with a change in appetite over days of treatment with Relief. A significant correlation between % patients with normal appetite and with a 15-day treatment was observed (dotted line; $r=0.777$, $p<0.001$).

Serum liver enzymes

Serum liver enzymes were performed on the patients before or at the beginning of their withdrawal and Relief treatment. The percent of patients having an abnormal serum level of any of the three liver enzymes tested (GGT, AST, and ALT) was 89.7%: (86.2% for GGT, 79.3% for AST and 75.9% for ALT). The mean values were 263 ± 79 , 116 ± 22 , 109 ± 27 U/L for GGT, AST, and ALT, respectively, which were ~3–5 times higher than the upper limit of the reference range. Following Relief administration, serum liver enzymes were performed for eight patients after two periods: 3–5 days and 9–15 days of treatment (Figure 4). The serum GGT, AST, and ALT enzymes were reduced by 38%, 56%, and 24% for the 3–5 day period and 51% ($p < 0.05$), 79% ($p < 0.05$) and 63% for 9–15 day period, respectively.

Quality of life, Bf-SR scale

The Bf-SR scale consists of 24 questions with three possible answers, rated with 0, 1 and 2. The highest possible scale is 48. High values represent an inadequate assessment of the quality of life and a reduction in the scale suggest improvement in the quality of life. Typical starting scale in depressed patients is around 30 and in patients with insomnia is around 25, however, after effective treatment values drop to ~15. In the present study, the Bf-SR starting scales were typical for neurological syndromes such as depression or insomnia and lowered (i.e. improved) during the treatment (Figure 4). The scales showed a trend of improvement at the beginning and significantly reduced to successful levels on the 7th day of treatment ($p < 0.05$) and kept low to the end of the treatment ($p < 0.001$) (Figure 5). Furthermore, the overall improvement was significantly correlated to the 15-day treatment with Relief ($r = 0.933$, $p < 0.001$).

Safety

During a 15-day, three capsules/day treatment, only 4 out of 32 subjects acquired adverse events. Two of which were expected characteristics of the herbal extracts in the study product (excretion of black cumin essential oils through the skin and effects on the digestive tract), whereas the other two adverse events are highly doubtful to be related to the study product. The adverse events are described as follows:

1. *Change of body odor*: One patient (male, 49 years old) reported a change in body odor. It started two days after Relief administration and lasted until the last study day. The patient had concomitant treatment for bronchiole asthma and ADHD. The reaction was not considered serious and the patient fully recovered. Changes of body odor may be expected with the intake of preparations containing *Nigella sativa* (black cumin). For some indications such as the use as a repellent a transdermal excretion of essential oil components it is even considered the mechanism of action. The above condition was not considered an adverse event, but a consequence of a normal metabolism.

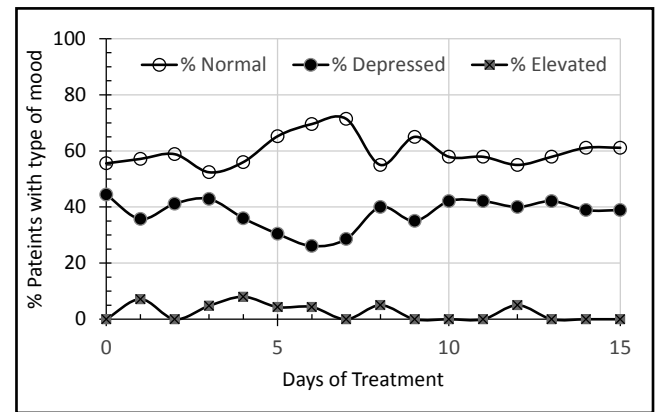


Fig. 3. The % patients with normal, low or high mood during a 15-day treatment with Relief.

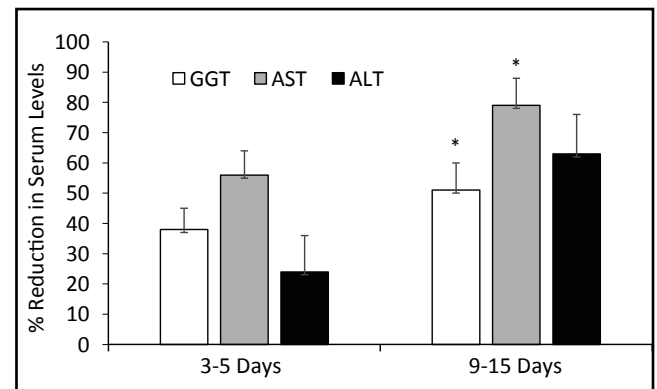


Fig. 4. The % reduction of serum liver enzymes following Relief administration at two different periods; 3–5 days and 9–15 days (* $p < 0.05$).

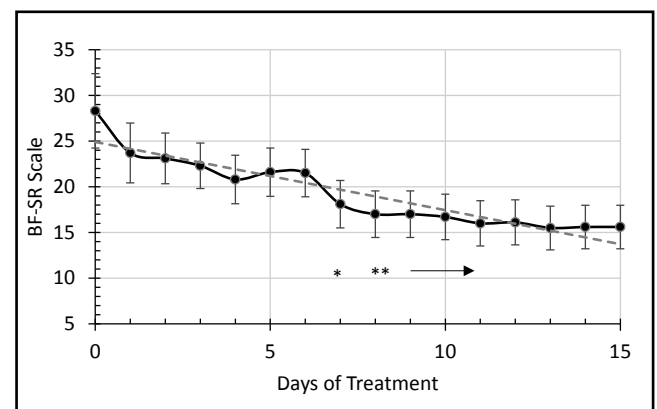


Fig. 5. The Bf-SR scale over days of treatment with Relief. On day 7, the Bf-SR scale became significantly different than the scale of 25 (according to the y-intercept regression line) (dotted line $r = 0.933$, $p < 0.001$; t-test: * $p < 0.05$, ** $p < 0.001$).

2. *Flatulence and burping*: One patient (male, 62 years old) reported the occurrence of mild flatulence and burping four days after the administration of the study preparation. The patient terminated the course of his detoxification after nine days. The reaction was not considered serious, and the patient fully recovered. There was additional medication, but no details were available

on the drugs taken. Causality was attributed to the study preparation and considered “probable.” In fact, the reaction could point to changes in the digestive system, as especially the spices (*Nigella sativa* – Black cumin and *Raphanus sativa* var. *niger* – Black radish) have effects on the intestinal tract which include carminative activity. The latter could lead to an increased expulsion of intestinal gasses and thus to flatulence during the time of adaptation of the digestive system under the impact of the herbal constituents on liver metabolism. The reaction is not necessarily an adverse event, as it may have been an expression of digestive efficacy.

3. *Exanthema of the face*: One patient (male, 34 years) complained about an exanthema on the face, occurring on the third day of therapy and lasting for two days. The patient discontinued the intake of the study preparation and the alcohol detoxification. Additional medication was involved, but no details are available. The patient fully recovered from the exanthema after that. The reaction was considered non-serious, and no causality assessment was made. Technically, the causality assessment would be “possible,” as a causality of the study preparation cannot be excluded. There are, however, many potential causes unrelated to the study preparation. Allergies to the herbal constituents were an exclusion criterion for study participation, and in any case, would a patient with hypersensitivity against any of the herbal components have reacted within 24 hours after first exposure. The fact that the exanthema only developed after two days points to a factor besides the study preparation, e.g., a contact allergy to the cleaning agents in the hospital, as one possible cause.

4. *Metallic taste*: One patient (male, 55 years) complained of “metallic taste” which started during the second day of treatment and lasted for two days. The patient discontinued the administration of the study preparation and further participation in alcohol detoxification. There was additional medication involved,

but no details are available. The patient fully recovered after that. No causality assessment was proposed by the physicians. Technically this case would be rated as “possible” as causality by the study preparation cannot be formally excluded. However, such reactions have never been observed with any of the herbal constituents of the study preparation despite an extensive experience with clinical exposure, the relation between metallic taste and the intake of the study preparation is not very likely. It may either have been a misinterpretation of the flavor of the aromatic herbs such as saffron or could have been related to the admission to the hospital and the sudden withdrawal of alcohol.

Global assessment of beneficial effects

The beneficial effects of the Relief were assessed as excellent in 68.8 % of cases, good in 15.6%, moderate in 12.5% and poor in only 3.1% (Figure 6). The majority (87.5%, n=28) of the subjects declared interest in reusing Relief for the next detoxification period.

DISCUSSION

The present study has shown that oral intake of the designed content of Relief could have a positive effect on the course of alcohol detoxification by reducing some of the AWS. These AWS are triggered when alcohol is withdrawn following long-term alcohol consumption because of the glutamate system activation in the brain. The latter system excites the CNS causing an imbalance in the neurotransmitter circuit resulting in AWS (Sachdeva *et al.* 2015). *Crocus sativus* (saffron) extract, which is one of the constituent of Relief, has been found to inhibit glutamatergic synaptic transmission in rat cortical brain (Berger *et al.* 2011). Another constituent of Relief is passion flower extract which has been found to minimize mice’s withdrawal anxiety in alcohol-addicted mice (Dhawan *et al.* 2002). Similarly, the preclinical studies of Relief have shown that extract reduced symptoms and behavior of alcohol dependence in mice suggesting its use as a therapeutic agent for medical management of alcohol dependence (Qadan 2014; 2015; 2017). The present pilot study has shown an improvement in the quality of life, and reduced some AWS such as hyperhidrosis and appetite after 6 to 7 days of treatment. On the other hand, the management of AWS such as anxiety, mood, headache, and consciousness was not conclusive for the following reasons: 1) limitations of the number of patients having the symptom and 2) a 15-day treatment may not be sufficient to modify AWS such as mood.

It has been known that treating chronic conditions usually takes longer medication time. In a randomized and double-blind clinical trial study, saffron supplementation statistically improved the mood and moderate depression in subjects (Akhondzadeh *et al.* 2005; Noorbala *et al.* 2005) and decreased opioid-temptation (Shahi *et al.* 2017). Another constituent of Relief is pas-

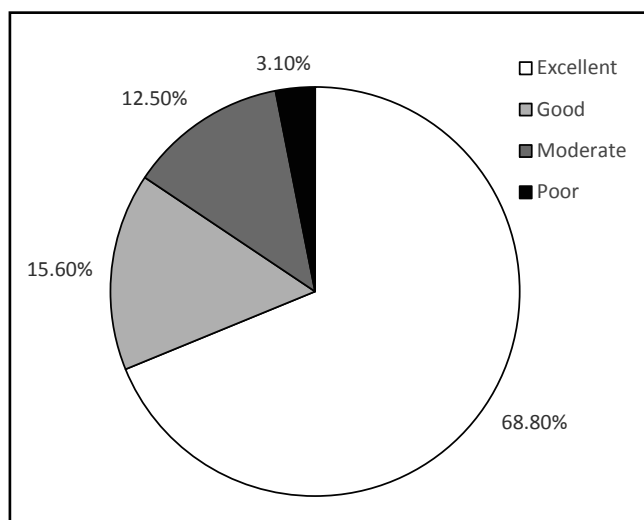


Fig. 6. Global assessment of Relief beneficial effects on AWS.

sion flower extract which has been found to improve patients' conditions with generalized anxiety disorder (Akhondzadeh *et al.* 2001). In the latter clinical studies, the treatment span was 4 to 8 weeks. However, it has to be mentioned that passion flower extract has been used to alleviate anxiety when given just before surgery (Movafegh *et al.* 2008; Appel *et al.* 2011; Aslanargun *et al.* 2012) and cocoa has been found to improve mood condition (Nehlig 2013). Similarly, in the present study, a severe case of anxiety was reduced to mild state after the first day of treatment, and the percent of patients with depressed mood significantly decreased in days 5 to 7 of treatment.

In the present study, serum liver enzymes were high in the majority (~90%) of the subjects, and this is mainly related to chronic alcoholism. Following Relief administration, serum liver enzymes were reduced by ~50–80% within two weeks. Two constituents of Relief, radish, and black cumin, were added to support liver functions (Al-Jenoobi *et al.* 2010; Evans *et al.* 2014). However, since alcohol administration has been withdrawn from patients and the current study is not controlled, we cannot predict superiority of Relief in protecting or supporting liver cells. On the other hand, since serum liver enzymes were significantly reduced within two weeks, this indicates the safety of Relief on liver cells and also it may predict that Relief facilitates faster healing of liver cells. The latter suggestion needs a controlled clinical study to confirm such indication.

The safety of Relief has been assumed to be high since the doses selected of each constituent has previously been evaluated in clinical trials and shown to be safe. In the present study, only two adverse events would be considered true adverse events, and even in these two cases the causality with the study preparation is highly doubtful. This is especially true for the observation on an exanthema on the face when it appeared two days after starting the administration of Relief. Overall, this study showed that the combination of the herbal in Relief is safe.

The limitations of the present study are distinct since it is a pilot, open-label prospective study with a small sample size. Since it is not a randomized control study and the sample size is small, the results should be cautiously interpreted. Despite that, the findings of this research, especially the quick and distinct improvement of the quality of life scale, justify further examination of the effects under controlled conditions. The percentage of ratings of the beneficial effects as "good" to "excellent" is characteristic for observational studies with efficient herbal medicinal products. Similarly, the readiness to use the study preparation again for future treatments is a positive signal. It might be necessary to prolong the exposure, as herbal constituents would not be expected to cause rapid effects on mood within a few days. Therefore, a full-scale well-controlled study design is warranted.

Conflict of Interest

The herbal combination presented in this study has been patented by one the authors (Fadi Qadan; Reference 24) EP2934561A1, US20150320815, 98210218, 9789145, WO/2014/097259A1 with the Arabian German Medical Products Co. W.L.L as an assignee. The other authors have no competing interest.

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