Journal of Ethnopharmacology 18 (1986) 229-243 Eleavier Scientific Publishers Ireland Ltd

PSYCHOPHARMACOLOGIC ANALYSIS OF AN ALLEGED ONEIROGENIC PLANT: CALEA ZACATECHICHI

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(Accepted October 8. 1986)

Summary

Calea zacatechichi is a plant used by the Chontal Indians of Mexico to obtain divinatory messages during dreaming. At human doses, organic extracts of the plant produce the EEG and behavioral signs of somnolence and induce light sleep in cats. Large doses elicit salivation, ataxia. Retching and occasional vomiting. The effects of the plant upon cingulum discharge frequency were significantly different from hallucinogenic-dissociative drugs (ketamine, quipazine, phencyclidine and SKF-10017). In human healthy volunteers, low doses of the extracts administered in a double-blind design against placebo increased reaction time end time-lapse estimation. A controlled nap sleep study in the same volunteers showed that Calea extracts increased the superficial stages of sleep and the number of spontaneous awakenings. The subjective reports of dreams were significantly higher than both placebo and diazepam, indicating an increase in hypnagogic imagery occurring during superficial sleep stages.

Introduction

Dreams are important in mesoamerican cultures. They are believed to occur in a realm of suprasensory reality and, therefore, are capable of conveying messages (Lopez-Auatin. 1980). The use of plant preparations in order to produce or to enhance dreams of a divinatory nature constitutes an ethno-pharmacological category that can be called "oneiromancy" and which justifies rigorous neuropharmacological research. There are several plants used in Indian communities of Mexico to obtain divinatory messages from dreams. Several puffball mushrooms (Lycoperdon spp.), wrongly reported as hallucinogens (Ott et al., 1975), are eaten fresh by Mixtec Indians before going to bed in order to dream (Diaz, 1975. 1979). Nahuatl Indians from the Sierra de Puebla use an as yet unidentified species of Salvia, known by the name of Xiwit, for the same purpose (Tim Knab, pers. commun.). The plant known as Bakana to the Tarahumara Indians, which has been reported to be an analgesic, antipsychotic and divinatory agent (Bye. 1979), was later found to be employed for dreaming during night sleep (William Merrill, pers. commun.).

Finally, Calea zacatechichi Schl. (Compositae) is used in the same context by the Chontal Indians of Oaxaca. C. zacatechichi is a plant of extensive popular medicinal use in Mexico (Diaz. 1976). An infusion of the plant (roots, leaves and stem) is employed against gastrointestinal disorders, as an appetizer. cholagogue, cathartic, antidysentry remedy, and has also been reported to be an effective febrifuge. With other aromatic Compositae, dry C. zacatechichi is used as insecticide (Diet, 1975). There is also some information concerning psychotropic properties of this plant that require further clarification (Schultes and Hofmann, 1973).

The pioneer study on the appetizer properties of zacatechichi, conducted at the Institute Medico Nacional of Mexico, mentioned some psychoactive effects (Sandoval, 1882). MacDougall (1968) reported that a Chontal informant knew that the leaves of the plant were to be either smoked or drunk as an infusion to obtain divinatory messages. Subsequent interviews with MacDougall's informant and active participation in ceremonial ingestion revealed that the plant is used for divination during dreaming (Diaz, 1975). Whenever it is desired to know the cause of an illness or the location of a distant or lost person, dry leaves of the plant are smoked, drunk and put under the pillow before going to sleep. Reportedly, the answer to the question comes in a dream. A collection of interviews and written reports concerning the psychotropic effects of these preparations on 12 volunteers has been published (Diaz. 1975, 1979). Free, reports and direct questioning disclosed a discrete enhancement of all sensorial perceptions, an increase in imagery, mild thought discontinuity, rapid flux of ideas. and difficulties in retrieval. These effects were followed by somnolence and a short sleep during which lively dreams were reported by the majority of the volunteers. These preliminary observations suggested that the psychotropic effects of the plant were similar to those interesting from ethnobotanical. psychological and neuropharmacological of the "cognodysleptic" drugs, whose prototype is marihuana (Cannabis sativa)(Diaz, 1979). The possible effects upon dreaming are the most perspectives.

C. zacatechichi is a shrub measuring 1-1.5 m in height. The plant has many branches with oviform and opposite leaves (3-5 cm long and 2-4 cm wide). The leaves show serrated borders, acute endings and a short petiole. They are rugose and pubescent. The inflorescence is small and dense (comprising around 12 flowers each) with the pedicels shorter than the heads (Martinet, 1939). The plant grows from Mexico to Costs Rice in dry savannas and canyons (Schultes and Hoffmann, 1973). The name of the species comes from Nahuatl "zacatechichi" which means "bitter grass' and is the common name of the plant all over Mexico. It is also known with the Spanish names of "zacate de perro" (dog's grass), "hoja madre" (mother's leaf) "hoja de dies" (Cod's leaf), and thle-pela-kano in Chontal Diaz, 1975).

Several sesquiterpene lactones had been isolated from the plant. Calaxin and ciliarin were identified by Ortega et al. (1970), and the germacranolides, 1B-acetoxy zacatechinolide and l-oxo zacatechinolide, by Bohlmann and Zdero (1977). Quijano at al. (1977. 1978) identified caleocromenes A and B and caleins A and B. while Ramos (1979) found caleicins I and II. Herz and Kumar

(1980) isolated acacetin, o-methyl acacetin, zexbrevin and an analogue, as well as several analogues of budlein A and neurolenin B, including calein A. C. zacatechichi samples show differences in chemical composition, which has led Bohlmann et al. (1981) to suggest that chemical taxonomy may help to reclassify the genus. Further taxonomic work is required since our Chontal informant distinguishes between "good" and "bad" varieties according to their psychotropic properties.

In the present paper we report some properties of zacatechichi extracts upon cat behavior and EEG, human reaction time, nap EEG, and subjective experiences.

Materials and methods

Plant collection and extract preparations "Good" samples of C. zacatechichi were collected under the guidance of the Chontal informant near Tehuantepec, Oaxaca during November, 1978. Specimens of this collection were identified by Dr. Miguel Angel Martinet Alfaro at the National Herbarium of Mexico as C. zacatechichi despite the Fact that there were minor morphological differences relative to previously collected material. The samples were identical with collections made in the area of the isthmus of Tehuantepec.

One kilogram of the dried plant (stem and leaves) was mashed and extracted with hexane until exhaustion in a Soxhlet apparatus. This fraction was dried and 308 of an solvent-free hexane extract were obtained. The remaining material was thoroughly extracted with methanol and the organic fraction evaporated. This procedure resulted in 86 g of a solvent-free gummy residue called the methanol extract. Both extracts were separated in fractions and packed in gelatin capsules for pharmacological experiments. The dose was estimated in the following manner: the human dose for divinatory purposes reported by the Chontal informant is "a handful" of the dried plant. Since the mean weight of many handfuls taken by several people was 60g we decided that the average human dose (HD-1) is around 1 g/kg of dried-mashed material. Therefore, the HD-1 for the hexane extract was 30 mg/kg, and 86 mg/kg for the methanol extract. In the experiments with cats. doses of HD-2. -4. -6 and -10 of both extracts were used. The EEG; effects of C. zacatechichi extracts were compared with those elicited by phencyclidine (Bio-ceutic Laboratories), quipazine (Miles Research Products). ketamine (Parke Davis) and SKF-10047 (Smith Kline B French), and industrial solvent toluene. which can produce the appearance of 6 cps spike and wave activity in the cingulum of cats. During the appearance of this electrographic activity animals show "hallucinatory" behavior (Conteras et al.. 1979, 1984).

Behavioral toxicology in cats

This first experiment was performed in order to assess the possible toxic behavioral effects of C. zacatechichi extracts. For this purpose three male

cats (3 kg each) were used. Observations were done from 1300 to 1500 h in a sound-attenuated recording chamber (109 x 76 x 74 cm) with a triple-glass wall. Each animal was placed in the cage and its behavior was recorded for 1 h prior to oral administration of a gelatin capsule (25 x 8 mm) containing a zacatechichi extract and 2 h thereafter. Each capsule was placed inside the mouth and swallowing was forced by giving 2-3 ml of saline solution. The extracts (methanol or hexane) and doses (HD-1, HD-2. HD-4. HD-10) were randomly assigned and tested only once. Two cats were observed three times and the third animal twice. Between tests each animal was allowed to rest for 6 days. Sampling ad libitum (Altmann. 1974) was used to evaluate the cats' response. Attention was given to abnormal behaviors such as ataxia, bizarre postures and movements directed to non-existing objects (Fischer. 1969).

EEG activity in cats

Several common EEG effects to a series of hallucinogenic compound have been reported by Winters et al. (1972). A dissociative action in multi-unitary activity between the reticular formation and basolateral amygdala and a hypersynchronic rhythm (2-3 cpa) in cortical recording are the two most characteristic features. Tracheal administration of neurotoxic industrial solvents produce limbic discharges while cats display "hallucinatory behavior" (Contreras et al., 1979). The following experiment was designed to ascertain whether C. zacatechichi extracts share these neurophysiological actions.

Six adult male cats were stereotaxically implanted with stainless steel concentric bipolar electrodes in the basolateral amygdala. the septum and cingulum according to the atlas of Snider and Niemer (1961). Epidural electrodes were placed on the cortex at the marginal circumvolution. After surgery the animals were allowed a & 1 week recovery period. Each cat was used as its own control and the effects of oral administration of zacatechichi extracts (HD-6) were compared to those of phencyclidine (400 ug/kg i.m.), quipazine (10 mg/kg i.p.), ketamine (6 mg/kg i.m.) and SKF-10047 (3 mg/kg i.m.). These drugs are dissociative psychodysleptics and produce 6 cps wave-and-spike activity in cingulum recording in addition to the characteristic hypersynchronic rhythm (Contreras at al., 1984). In each experiment, control recordings were taken in addition to at 60 min and + 120 min after drug administration.

Reaction Time and Time-lapse estimation in humans

Measurement of reaction time to a light flash and the ability to calculate fixed lapse times in humans allows the identification of hypnotic compounds (Fernandez-Guardiola et al., 1972). Objective evaluations of time perception modification by marihuana have been achieved with the same technique (Fernandez-Cuardiola et al., 1974). From the experiments performed in cats it appeared that zacatechichi had hypnotic properties. Therefore, we chose this experimental paradigm to evaluate human effects. The study was performed in

5 healthy volunteers (3 women and 2 men. ages 23-34) according to the procedure described by Fernandez-Guardiola et al. (1972, 1974). The subjects were informed about the experiment and the known effects of the plant and a written consent was obtained. Capsules containing either a Calea extract (HD-1) or placebo were administered 1 H before the task in a double-blind randomized design, where neither the volunteers nor the evaluator knew which substance had been ingested. The first session did not involve the administration of any substance in order to habituate the subjects to the experimental manipulations. Physiological responses recorded included EEG, electromyogram, electrocardiogram, and galvanic akin response. All sessions were done at the same time period (1700-1820 h). A complete session consisted of alternated 10-min periods for reaction-time evaluation and 10-min periods for time-lapse estimation. In the reaction-time periods the subjects were instructed to press a button with their dominant hand as soon as possible after a light wee dashed. Intervals between consecutive dashes were of 10-s duration. In the following 10 min, alternating with the reaction-time periods, the subjects were asked to estimate the dash intervals by pressing the button each time they thought the light should have been dashed. The entire test lasted 80 min. Analysis of variance was used to assess results between and within individuals, the protected "t" and Least Significant Difference tests were used in paired comparisons.

Sleep recordings in humans

The conventional procedure for EEG recording of sleep (Rechtschaffen and hales. 1968) was used in a similar double-blind randomized design which in this case, included a low dose of an active hypnotic drug (diazepam, 2.5mg orally). In order to standardize the nap session, all volunteers were asked to reduce their normal sleep time by 2 h the night before testing. The extract, diazepam or placebo capsule was ingested 1 H prior to the recording session (1700-1900 h). The physiological variables recorded included respiratory and heart rates, number of nap episodes, total time spent in wakefulness (W). in slow wave sleep stages (SWS stages I to IV) and in rapid-eye-movement sleep (REM) (Rechtschaffen and Kales, 1968). The respiratory rate was recorded by means of a thermistor located in the nostril and connected to a polygraph amplifier measuring the air temperature in each inhalation-exhalation cycle. This is an indirect method which provides the frequency and amplitude of respiratory rate. Data analyses were done by means of factorial analysis of variance (ANOVA). For paired comparisons, the Student Newman-Keuls test was used.

Dream reports

The psychological effects of Calea extracts were evaluated by the application of directed questionnaires and analysis of free reports of the subjective sensations and dreams in all human volunteers after the reaction-time, nap sessions and the following night. Neither the subjects, the interviewer nor the evaluator knew whether the individual had taken a plant extract,

diazepam, or placebo. The results were compared by the binomial test.

Results and discussion

Behavioral toxicology in cats

Some minor behavioral changes were observed with low doses of both extracts (HD-1 and HD-2). The cats stared for long periods of time and 30 min after the administration of the zacatechichi extracts somnolence and sleep were frequently observed. The HD-4 and HD-1O doses of the hexane extract produced ataxia, bilateral contractions of nasal and maxillar muscles, and stereotyped pendulum head movements. The HD-10 dose also induced salivation with vomiting occurring about 90 min after administration. The methanol extract produced ataxia (HD-4) and compulsive grooming (HD-2). A common toxic effect of both extracts (doses HD4 and HD-10) was retching and thick salivation.

It was not clear if these effects were elicited by direct central nervous system stimulation or in response to local gastric irritation caused by some bitter principle of the plant. This activity was noted by Giral and Ladabaum (1959) and may be responsible for the appetizer properties of C. zacatechichi. Stare and pendular head movements can be elicited by several psychoactive drugs such as toluene (Alcaraz et al., 1977; Contreras et al., 1977), quipazine (Sales et al.. 1966, 1968) and dopamine agonists (Ernst.1967). These effects are. therefore, not specific for any one of the several classes of psychoactive compounds. Moreover, staring and pendular head movements may merely be indications of somnolence. In order to analyze more precisely the neural effects, electrophysiological recordings were taken in free-moving cats.

EEG activity in cats

Both plant extracts produced similar EEG changes which were very different from the other drugs used. The hexane extract induced 3 cps large voltage rhythms in the cortex, cingulum and septum while the methanol extract provoked 8 slowing of the EEG rhythm more predominant in subcortical structures. Somnolence was observed during the appearance of these changes. A quantitative analysis of frequency of discharge in the cingulum was performed for all drugs tested. The hexane extract produced only minor changes while the methanol extract clearly decreased the frequency. This response is in contrast to the known psychodysleptic compounds which produce decreases of 6-7 cps (Contreras et al., 1984).

The results of these experiments show that zacatechichi does not share the neurophysiological effects of the dissociative psychodysleptics and only induces the behavioral and EEG signs of somnolence and sleep. The apparent low toxicity of the plant in these experiments and its history of ethno-botanical use allowed us to ascertain the hypnotic potency, dream-inducing effects and other psychotropic properties in human beings. Reaction time and time-lapse estimation in humans. No differences among the three treatments

were found for human rate, galvanic skin response and EEG recordings. With the methanol extract, short periods of sleep (stage I) usually appeared between flash intervals, and the subjects were awakened by the light. Both extracts produced a statistically significant slowness of reaction-time: 250 ms with placebo, 280 ms with hexane extract and 290 ms with methanol extract ($P < 0.01$). Similarly, the IO-s lapse was overestimated with the zacatechichi extracts. The methanol extract increased estimation by 3 s on average ($P < 0.001$). Both extracts increased respiratory rate, but this change was not significantly different from controls.

The characteristic EEG slowness and the increased reaction times of subjects treated with both extracts suggested that zacatechichi may contain hypnotic compounds. Moreover, a larger effect was elicited by the methanol extract suggesting that the active compounds might be found in the polar fractions. An increase in time-lapse estimation and a weak respiratory analeptic effects have been reported after marihuana administration (Fernandez-Guardiola et al., 1974).

Sleep recordings in humans

Since the experiment just discussed did not allow an analysis of sleep stages, the possibility of sleep and dream modifications by zacatechichi was tested in a nap study conducted in the same human volunteers. Heart rate, total time and frequency of each stage of sleep did not change with any treatment in comparison to placebo (Fig. 5). However, it was found that the frequency of W and SWS-IV stages were significantly modified by treatments ($W\ F(3,32)= 5.28$, $P < 0.01$; $SWS\text{-}IV\ F(3,32) = 3.35$. $P<0.05$). Post-hoc paired comparisons showed that, upon onset of sleep, the methanol extract and diazepam increased significantly the frequency of W stages ($P < 0.05$) when compared to placebo. In contrast, methanol extract and diazepam decreased significantly ($P < 0.05$) the number of SWS-IV stages. The other stages of sleep were not significantly modified by treatments, SWS-I and SWS-II showed a alight increase in comparison to placebo and, in contrast, SWS-III and REM stages decreased slightly. Respiratory rate was significantly modified by treatments ($F(3,400)=79.92$, $P < 0.005$). Paired comparisons showed that the methanol extract increased ($P < 0.05$) when compared to all other treatments. Although this small increase may lack physiological relevance, it does suggest a pharmacological effect upon respiratory rate. These results support the idea that zacatechichi extracts, particularly the methanol fraction, contain compounds with activity equivalent to sub-hypnotic diazepam doses. Ingestion of the plant produces a light hypnotic state with a decrease of both deep slow-wave sleep and REM periods. The question of the ethnobotanical use and open trial reports of dream enhancement was studied in the following section by the evaluation of subjective reports during the sleep study.

Dream reports

The quantitative results concerning hypnagogic imagery and dreams are

summarized in Table 1. Data from the reaction-time and the nap sessions end the following night were pooled. Significantly more dreams ($P < 001$, in comparison to placebo) were reported after the methanol extract. Similarly, the number of dreams reported during naps was significantly higher following the administration of the plant extracts than with diazepam ($P < 0.01$). It can be appreciated that, although not significant, the number of dreams reported was greater after the ingestion of Calea extracts than placebo. A more detailed analysis of dream content is shown in Table 2. The number of subjects that did not remember dreaming was always greater after placebo and diazepam administration and. conversely, the individuals that reported more than one dream per session were always the ones treated with zacatechichi extracts. The dreams reported by subjects ingesting Calea extracts, were of a shorter content (measured by the number of lines written in the report). Spontaneous reports of emotions and nightmares were not different among the four treatments. Nevertheless, with the methanol extract more colors during dreaming were mentioned. These results show that zacatechichi administration appears to enhance the number and/or recollection of dreams during sleeping periods. The data are in agreement with the oneirogenic reputation of the plant among the Chontal Indians but stand in apparent contradiction to the EEG sleep-study results. It is well known that dreaming activity is correlated to the REM or paradoxical phase of sleep (Aserinsky and Kleitman, 1953) and it could be expected that a compound that increases dream would also increase REM stage frequency or duration, as it has been shown to occur with physostigmine (Sitaram et al., 1978). In contrast, zacatechichi increases the stages of slow wave sleep and apparently decreases REM sleep. This also occurs with low doses 12-10 mg) of diazepam (Harvey, 1982). Despite this similarity in EEG effects, diazepam decreases dreaming reports (Firth, 1974) while zacatechichi extracts enhances them. Such discrepancy may be explained by the fact that dreaming and imagery are not restricted to the REM episodes but also occur during slow wave sleep (SWS I and II) as lively hypnagogic images (Roffwarg et al., 1962). Such images are reported as brief dreams and are known to be enhanced by marihuana (Hollister, 1971). All this suggests that Calea zacatechichi induces episodes of lively hypnagogic imagery during SWS stage I of sleep, a psychophysiological effect that would be the basis of the ethnobotanical use of the plant as an oneirogenic and oneiromantic agent.

Acknowledgments

The authors wish to express their gratitude to Dr. Alfredo Ortega for advice in the preparation of the plant extracts.

References

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