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Ethnobotany of *Plectranthus neochilus* Schltr (Meprobamate) in Cuba

[Estudio etnobotánico de *Plectranthus neochilus* Schltr (Meprobamato) en Cuba]

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Abstract: Chloroform extract (CE) and fractions obtained from *Aldama arenaria* roots were evaluated for their *in vitro* antiproliferative activity against 10 human tumor cell lines [leukemia (K-562), breast (MCF-7), ovary expressing a multidrug-resistant phenotype (NCI/ADR-RES), melanoma (UACC-62), lung (NCI-H460), prostate (PC-3), colon (HT29), ovary (OVCAR-3), glioma (U251), and kidney (786-0)]. CE presented weak to moderate antiproliferative activity (mean log GI_{50} 1.07), whereas fractions 3 and 4, enriched with pimarane-type diterpenes [ent-pimara-8(14),15-dien-19-oic acid and ent-8(14),15-pimaradien-3β-ol], presented moderate to potent activity for most cell lines, with mean log GI_{50} of 0.62 and 0.59, respectively. The results showed promising *in vitro* antiproliferative action of the samples obtained from *A. arenaria*, with the best results for NCI/ADR-RES, HT29, and OVCAR-3, and TGI values ranging from 5.95 to 28.71 µg.ml^{-1}, demonstrating that compounds of this class may be potential prototypes for the discovery of new therapeutic agents.

Keywords: *Aldama arenaria*; Antiproliferative activity; Ent-pimara-8(14),15-dien-19-oic acid; Ent-8(14),15-pimaradien-3β-ol; Pimarane; *Viguiera arenaria*.

Resumen: El extracto de cloroformo (CE) y las fracciones obtenidas de las raíces de *Aldama arenaria* fueron evaluadas por su actividad antiproliferativa *in vitro* contra 10 líneas celulares tumorales humanas [leucemia (K-562), mama (MCF-7), ovario que expresa un fenotipo resistente a múltiples fármacos (NCI/ADR-RES), melanoma (UACC-62), pulmón (NCI-H460), próstata (PC-3), colon (HT29), ovario (OVCAR-3), glioma (U251) y riñón (786-0)]. CE presentó actividad antiproliferativa débil a moderada (log GI_{50} promedio de 1.07), mientras que las fracciones 3 y 4, enriquecidas con diterpenos de tipo pimarane [ent-pimara-8 (14), ácido 15-dien-19-oico y ent-8 (14), 15-pimaradien-3β-ol], presentaron actividad moderada a potente para la mayoría de las líneas celulares, con un log GI_{50} promedio de 0.62 y 0.59, respectivamente. Los resultados mostraron una prometedora acción antiproliferativa *in vitro* de las muestras obtenidas de *A. arenaria*, con los mejores resultados para NCI/ADR-RES, HT29 y OVCAR-3, y valores de TGI que van desde 5.95 a 28.71 µg.ml^{-1}, lo que demuestra que los compuestos de esta clase pueden ser prototipos potenciales para el descubrimiento de nuevos agentes terapéuticos.

Palabras clave: *Aldama arenaria*; Actividad antiproliferativa; Ent-pimara-8 (14), ácido 15-dien-19-oico; Ent-8 (14), 15-pimaradien-3β-ol; Pimarane; *Viguiera arenaria*.

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INTRODUCTION

In the underdevelopment countries, the medicinal plants result a valuable resource of its health systems. Even when there is no a precise way to estimate the worldwide use of medicinal plants, the World Health Organization (WHO) has calculate that approximatelya 80% of the worldpopulation use the traditional medicine in the primary healthcare. In this estimation, the phytotherapy highlights by it prevalence, using not only plant extracts but also their isolated compounds (Giraldo *et al*., 2009)

The ethnobotanic is the science that study how the plants are used in the differentcultures by the population with independency of the type of society (Bermudez *et al*., 2018). This allows documenting valuable information which could be the basis knowledge necessary to develop new herbal remedies, and at the same time to evaluated their riskiness degree of those used plants. By this way, it will possible to design and establish programs for it conservation, contributing to the protection of the biodiversity (Pérez *et al*., 2011).

Species from Lamiaceae family are worldwide used due to their multiple properties. It includes flower plants belonging to the Lamiales order, integrated by 245genusand around 7900 species, turning in one of the largest groups of plant kingdom. *Plectranthus* L'Hér.genus comprises approximately 350 species of herbs and perennial shrubs native from the tropical regions of Africa, Asia and Australia. *Plectranthus* name comes from the Greek words *plektron* (sporon) and *anthos* (flower), illustrating one of the most common characteristics of the species from this genus (Méndez & Rifá, 2016)

In Cuba, until 2016 it was recognized the presence of three *Plectranthus* species: *P. amboinicus* (Lour.) Spreg., *P. scutellarioides* (L.) R. Br. and *P. verticillatus* (L. f.) Druce (Greuter & Rankin, 2016). Nevertheless, in 2016 was informed the extended cultivation in all Cuban provinces of other two species not previously described in Cuba: *Plectranthus neochilus* Schltr. and in less extension *P. barbatus* Andrew. The rapid widespread of this plant in Cuba was motivated in the first moment by the "Urban Agriculture Movement" (Méndez & Rifá, 2016), later on due to the increasing interest of the Cuban population in consuming extracts from *P. neochilus* with sedative and hypnotic purposes.

Original from the African continent, ***P. neochilus*** Schltr. is widely distributed and consumed in South American countries; nevertheless, the ethnobotanic information about this species is not referred as sedative. Neither was found in the scientific literature any paper who relates the validity of this specie to treat anxiety disorders.

A recent study conducted by Heredia *et al*. (2018) shows that in the northeast region of Cuba 16 species of plants are used for this purpose. *Justicia pectoralis* Jacq. stands out as the most used, relegating others like the *P. neochilus* (with an 85% fidelity index classifying like second for this parameter) to a secondary level. However, while *Justicia pectoralis* Jacq shows enough scientific and ethnobotanical references to support its use, *P. neochilus* lacks of such indicators.

Due to the recent introduction of this species and considering the non-existence of ethnobotanical and ethnopharmacological studies that guarantee the effective and safe by the Cuban population; the purpose of this research was to investigate deeply the ethnobotanical use that of this species do the Cuban population

MATERIAL AND METHODS

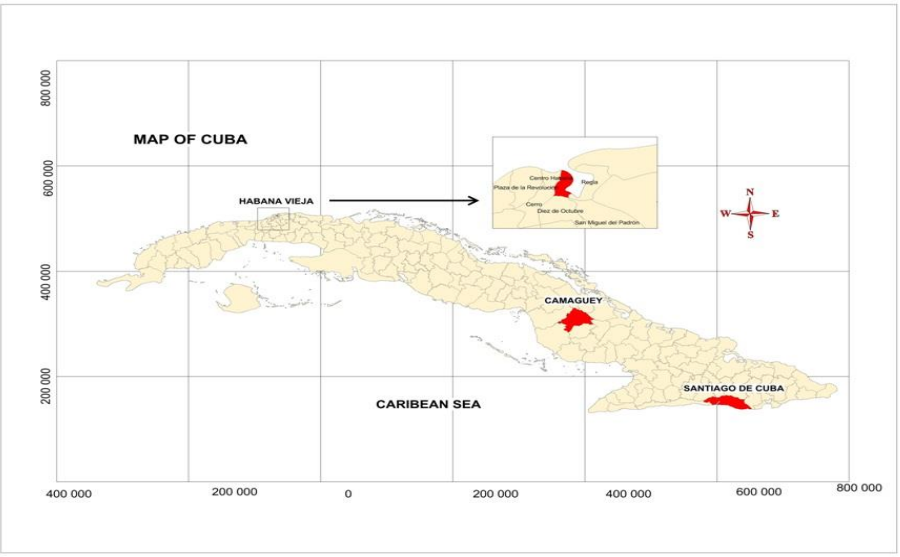
General overview

This study was divided in two parts:the first one consistent in a descriptive and retrospective bibliometric analysisusing the professional software Harzing´s Publish or Perish5 and as keyword *P. neochillus* and it botanical synonyms, while the second one consisting in adescriptive and transversal ethno-botanic study about the specie considering the three different regions of Cuba.

For the bibliometric analysis study developedit was considered all the published articles until December 2018 using "Google academic" as data base, classifying the results in two kinds of papers: Those with ethno-botanic information, and those with chemical and/or pharmacological experimentation, especially those related with the Central Nervous System. It was consideredalso as output variables the total number of papers andmain countries using and investigating the plant.

The ethno-botanic study encompassed the period from January 2017 to May 2018 and included 500 surveyed belonging of each one to the three geographic regions of Cuba, for a full-on of 1500 interviews. The Western Region was represented by inhabitants of the Center Havana's municipality; the

Central Region for the Camagüey municipality, while the Oriental by Santiago de Cuba municipality (Figure No. 1). Those municipalities were included because their higher level of inhabitants as well as their ratios in the consumption of medicinal plants. It was combined different qualitative and quantitative methods and techniques of this kind of research.



***WGS84 projection (EPS 64326) MapInfo Professional software version 12.0**
Figure No. 1
Cuban municipalities considered in the ethnobotanic study*

The fieldwork was performed by three specialists with experience in the field of medicinal plants and community work, trained in communication techniques and collection of ethno-botanical information.

Description of the study areas

Centro Havana municipality belongs to the province Havana, Cuba. Located in the north and central part of the province and in the west of the bay, it borders up on North with the Florida Strait, at south with Cerro, at east with HabanaVieja and at west with "Plaza de la Revolución) municipalities. Count with 3.42 km's territorial extension and a population of 140 233 inhabitants, being the municipality with higher population density (ONEI, 2016).

Camagüey municipality belongs to the province of the same name with a superficial extension of 1 098.58 Km^2 and a population of 326 743 inhabitants. To the north border with Esmeralda and Sierra de Cubitas municipalities, while at south with Jimaguayú, at east with Mins and Sibanicú and at west by Vertientes and Florida municipalities (ONEI, 2016). At last, Santiago de Cuba is the main municipality of a province with the same name. Reaches an extension of 1.031,74 km^2 and a population estimated in 510.563 inhabitants. Located at the south side of the island facing the Caribbean Sea bordered at north with San Luis and Songo La Maya municipalities. To the west with Guamá and Palma Soriano municipalities while to the east with Niceto Pérez, a municipality of Guantanamo Province (ONEI, 2016).

Universe and test sample

The universe of study was constituted by all the inhabitants of the communities and neighborhoods of the municipalities previously selected. The sample was selected through consecutive non-probabilistic sampling including people of both sexes, different ages, traditional healers, housewives, retirees, students and professionals dealing with medicinal plantsin the study areas that desires to cooperate of willful way in investigation and that they know or they had heard talkabout the species under consideration.The informed consent in written for all face to face quizzed and especially of the key interviewees (traditional healers and professional

dealing with medicinal plants) included in the samplewas obtained, respecting the principle of autonomy and guaranteeing the confidentiality of its participation.

Data collection

Data information was collected following the requirements established in the "Traditional Medicine in the Islands" (TRAMIL, 2018). It was usedan interview based on a designed semi-structured questionnaire elaborated on the basis and criteria of the objectives of this research, collecting two kinds of variables: socio-demographic and ethno-pharmacologic. The socio-demographic variables includes sex, scholar level, occupation, and age; while the ethno-pharmacologic variables includes medicinal uses of the specie, part of the plant used, methods and ways of preparation, concentration or plant/solvent ratios, times and consumption frequencies, side effects noted and concomitant consume with conventional drugs with actions on the Central Nervous System.

The used criteria to define the medicinal uses indicated by the interviewees were based on the testimonies of the participants and the diseases referred by them, to be later classified according to the pharmacologic category.

Plant authentication

Plants were collected and identified in the three herbariums corresponding to each Cuban region of the study: The National Institute of Ecology and Systematic (Western region), theHerbarium Julián AcuñaGalé of University of Camagüey (Central region) and the Herbarium Jorge Sierra Calzado at the Eastern Center of Biodiversity and Ecosystems (BIOECO) in the Eastern region of Cuba. The collected plants were processed before 48 hours to facilitate its morphologic and anatomic recognition with the help of keys and pattern samples comparison. Afterwards, they werebotanized following the habitual protocols of pressing and drying, to conserve in this last herbarium (BIOECO) the voucher specimen with 147 as code.

The authenticity of the plant material used by each informant was cross-checked when the interviewer showed a sample of the plant material and once confirmed by the interviewee, this one shows (in the possible cases) the source where he takes the plant for its consumption, being confirmed this time by the interviewer.

Qualitative analysis

The ethno-botanic information offered by each interviewee was organized in an excel sheet to be later on processed in the statistical package IBM SPSS Statistics 20 version 2.1. The comparisons between the three regions for the parameters with binomial nature (sex and cause of the combination of the plant extract with synthetic drugs) came true using the Chi-Square test for independent samples. For those parameters that considers multiple response options was used the test for medians comparison of Kruskal Wallis. Mathematical correlations between those variables that could be correlated (ie. concentration *versus* frequency and consumed quantities) was done using the Pearson correlation test. All test were running using the before mentioned statistical package and considering a 95.0% of confidence level.

Quantitative analysis

The use of quantitative indices in ethno-botanical research was calculated informing the use value (UV) and the Level of Significant Use of Tramil (UST) (Pérez *et al*., 2011).

Use value index (UV)

$$IVU = \frac{\sum Uvis}{N_{is}}$$

where:
Uvis: Number of uses mentioned by each informer
N_{is}: Number of interviewed persons.

Level of Significant Use of Tramil (UST)

$$UST = \frac{Use}{N_{is}} * 100$$

where:
Use: Number of summonses for a specific pharmacologic activity.
N_{is}: Number of interviewed persons.

RESULT AND DISCUSSION

As a result of the bibliometric analysis, a total of 51 articles were detected, of which 45 were related to: the ethnobotanical information or to the chemical/pharmacological profile. The other six

articles no associate with those categories were related to agronomy and/or botanic information. The papers linked with the ethnobotanic uses were 19, while 26 were related to chemical and/or pharmacological evaluations. The countries more focused on the research on chemical and/or pharmacological profiles were Brazil and Portugal, while on ethnobotanic profile were Brazil, Venezuela and South Africa by this order. As important observation, standout than in the opinion none of the pharmacologic nor ethnobotanic papers refers a sedative and/or hypnotic activity, whit the only exception of the ethnobotanic study developed in the northeast region of Cuba (Heredia *et al*., 2018).

As a result of the interviews fulfilled in the three areas under consideration the feminine sex prevailed with 1001 informers, representing 66.73% of the studied population (1500). This result can be associate to the role played by women in the society, specifically in the family care, and in the rescue of herbalist's traditional preparations for the treatment of common ailments. Additionally, the double workload (at home and at the traditional job) leads many to a continued stress, affecting the sleep levels of them.

Age groups holding higher information regarding the plant use were group 2 (38-59 years old, 46.33%) and the group 3 (> 60 years old, with 38.67%), representing the 85% of the all interviewed population.The knowledge of the species for these elderly groups can be related to that at these ages it is appealed to the use of the medicinal plants like therapeutic alternative to treat the stress generates by the workaday. At those ages also begin the clinical appearance of signs and symptoms of diseases correlated to the Central Nervous System entailing alteration on this like sleep disorders. In fact, group 2 encompass people that generally are of centre of the family, offering attention to parents and children's, doubling their familiar tasks increasing by default their stress and in consequence the insomnia.

Most of the people interviewed belong to the university level of scholar (663 representing a 44.20%), followed by those with technician level (399 for a 26.60%). At the same time, most of the informers were workers in concordance to the age of the interviewees. The high scholar level of the polled people is in conformity with the levels reached by the Cuban society by the social programs implemented after the 1959 revolution. All those demographic results are in agreement with previous studies developed by other ethno-botanic surveys developed in different regions of Cuba (Beyra *et al*., 2004; Pérez *et al*., 2011; Bermúdez *et al*., 2018) in which females with age around 40 to 60 years old and with university level are majority. Also in other Latin-American regions, women represent the better informers relating the use of medicinal plants, suggesting their higher knowledge connected to their daily activities (Roque *et al*., 2010; Silva & Freire, 2010; Madaleno, 2011; Zambrano *et al*., 2015).

The last one of the socio-demographic variables considered was their occupation at the moment when they fulfill the survey. The 70.80% of the interviewee were workers, representing 45.33% of them employees by companies of the Government while the independent labor force (private activities) reaches the 25.47%. A minor proportion (438 interviewed, 29.20%) were or housewives, retirees or students.

The 100% of the 27 traditional healers interviewed showed a high knowledge about the use of *P. neochillus* with medicinal intentions; in contrast to the percentage (32.07%) of the 106 health workers surveyed.In this cohort of persons (27 traditional healers and 106 health workers) only nine of the interviewees knew or had read about the demonstrated pharmacologic properties and it existence of references about it toxicity of the plant. That is why the staff confided to apply this interviews accomplished actions related to the qualification toward the knowledge increment about the use of this plant by the traditional healers and health workers. Also to observe with more details and interest the aspects correlated to the use of this medicinal plant, considering the role that they play in the health provision to the population.

In none of the socio-demographic variables it was found statistic differences between the three regions of Cuba studied considering the Kruskal-Wallis median comparison test at 95% of confidence.

Table No. 1 summarizes the uses that Cuban population does with the species under evaluation. In total, more than 3060 uses were reported, which means more than two pharmacological uses per person interviewed. The most referred uses are the association sedative/hypnotic. Curiously, these two activities have never been informed previously in none of the ethnobotanic studies outside Cuba as reveal the bibliometric study, while only in the paper published by Heredia *et al*. (2018), denoting that the

sedative/hypnotic use is particularly done by Cuban population but not by people from other latitudes. This confirm the link between the common name attributed to the plant by the Cuban population (Meprobamato), a synthetic anxiolytic that was withdrawn from distribution in Cuba in 2011 and it ethnobotanical use.

Table No. 1
Ethnobotanic uses that Cuban population makes with the plant species *Plectranthus neochilus* Scrthl.

	West	Centre	East	Frequency	Percent (%, based 1500)
Sedative	**312**	**323**	**349**	**984**	**65,60**
Hypnotic	**272**	**285**	**295**	**852**	**56,80**
Analgesic	**210**	**201**	**223**	**634**	**42,27**
Anti-inflammatory	**108**	**147**	**157**	**412**	**27,47**
Decorative	**52**	**33**	**49**	**134**	**8,93**
Anticatarrhal	**0**	**21**	**0**	**21**	**1,40**
Digestive affections	**0**	**23**	**0**	**23**	**1,53**
Total	**954**	**1033**	**1073**	**3060**	

In addition to these two main activities, other actions no pharmacologically related were frequently informed in the three Cuban regions: the analgesic and the anti-inflammatory. The analgesic effect was experimentally demonstrated as efficiency in the control of post-operatory pain in female cats submitted to ovary-salpingo-hysterectomy (Silva *et al*., 2013), while de anti-inflammatory activity was reported in many species of this botanical gene for example: *P. scutellaroides* (Cretton *et al*., 2018) and *P. amboinicus* (Arumugam *et al*., 2016), this effect can be related to the presence of several chemical compounds as amyrin (Nogueira *et al*., 2019) and flavonoids (Spagnuolo *et al*., 2018).

Table No. 1 also denotes that in the Central region, some uses are not informed in the other two regions as the anti-catarrhal and in digestive affections. These activities were previously informed declaring it use to treat digestive disturbances, pain, edema, skin infections and respiratory ailments (Caixeta *et al*., 2011; Madaleno, 2011). Daio *et al*. (2017) reported the maceration of the leaves *Plectranthus neochilus* Schltr. is a tonic to the gallbladder stimulating the secretion of bile, favoring the digestion of fats. Also, an ethno-medicine survey in South Africa revealed this species for treating respiratory infections (York *et al*., 2011).

At the same time, in Table No. 1 can be observed that the inhabitants of the Eastern region attribute a bigger number of properties to this species, followed by the central and western region respectively. However, there are no statistical differences between regions judging by the results of the comparison test of the median of Kruskal-Wallis at 95% confidence, which shows that the use of this medicinal plant in Cuba is the same with the independence of the region where it is consumed. By this way, these results confirm the unique observations that the Cuban population use *P. neochillus* mainly by it sedative and hypnotic properties.

Regarding to the part of the plant used, the 100% of the population refers the use of the aerial parts. The 58.66% use the stem and leaves, while the 42.33% uses the leaves only. Only five informants refer the use of the stem alone, mainly those associates to digestive disorders. Once again, and with independence of the numeric differences, none statistic differences were detected.

In Figure No. 2 are represented the preparation mode in which the population use the plant with medicinal purposes. Decoction is the most

used (77.67% of the interviewed) with independence of the region followed by the infusion 15.40%. The rest of the preparation modes were irrelevant with very low ratios of use. Once again, no statistic differences were found.

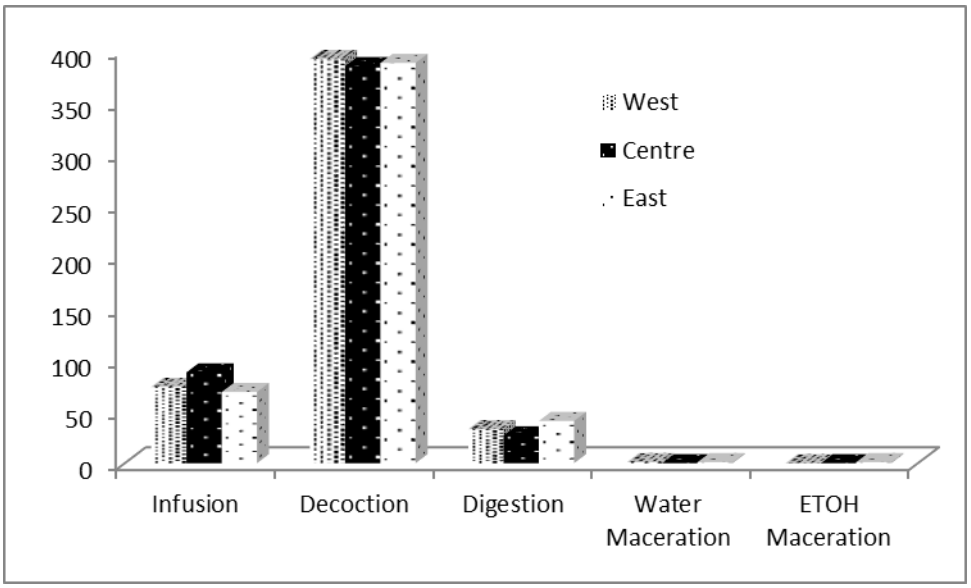


Figure No. 2
Modes of preparation of *P. neochillus* brew with medicinal purposes by the Cuban´s population

The informers that use the leaves and or the aerial parts of the species (1483) were mainly divided between those who add quantities equivalent from 10 until 20 leaves with or without stems to prepare one liter extract, representing the 44.77% and those who use from five to ten leaves (38.10%). Values fewer than five leaves per liter of brew has been not informed while those who use more than 20 leaves reaches the number of 224 representing the 15.10% mainly concentrated in the western region of Cuba, but without statistic differences.

This extract is consumed preferentially in a milk cup with an equivalent volume around 200 to 250 milliliters, during the night time half an hour before to sleep, (45.27%), while a 38.07% (571 interviewee) takes it in a coffee cup with an equivalent volume from 50 to 75 milliliters. A strong relationship between the concentration of the brew and the quantity consume was found with a correlation coefficient of r=0.76. In general sense, the 95.53% of the interviewees refers to consume the medicinal beverage only one time in a day before to sleep, inferring themselves that the concentration and amount intake are strong enough to evince the pharmacologic desired effect.

In Figure No. 3 it can be observed the main side reactions declared by the consumers of extracts from *P. neochillus.* Even when the population in general trends to consider the natural medicines as non-toxic, the interviewers notified 229 side effect reactions asserted by 141 informers. The common ones were vomiting (5.33% and laziness (4.87%), followed by headache, morning dry mouth, collywobbles and loss of the orientation with 31, 27, 10 and 8 informers respectively. A weak mathematic correlation (r=0.53) between the appearance of these side effects and the concentration of the extract was found. Nevertheless, only four over the 141 informers that refers any kind of side effect, drank the plant extract at the lower concentration (from 5 to 10 leaves per liter of formulation). These side effects referred before, are quite common for those synthetic drugs that acts over the Central Nervous System, especially the Benzodiazepines (Griffin *et al*., 2013).

The concomitant consumption of *P. neochillus* extracts with synthetic drugs was another

of the variables explored in this investigation. The results presented in the figure 4 express that 35% of the interviewees have used at least once both types of medication: Natural and Synthetic ones, being the group of the benzodiazepines the one with greater frequency. Curiously, synthetic analogue (Methylcarbamol) that belongs to the same chemical and pharmacological family from which the *P. neochillus* takes their common noun (*meprobamato* in Spanish) it is the one with smaller incidence (28 reports). Again, no significant differences between the kind of drug used and the studied regions were observed. Strong correlation between concomitant consumers (natural and synthetic) and side effects was also observed, with 97 from 141 informers having declared some side effect. These observed adverse effects should alert patients, pharmacists and doctors, since the relatively high average times and distribution volume of most of the anxiolytic drugs and especially the benzodiazepines ones; constitute one of the main sources of intoxication.

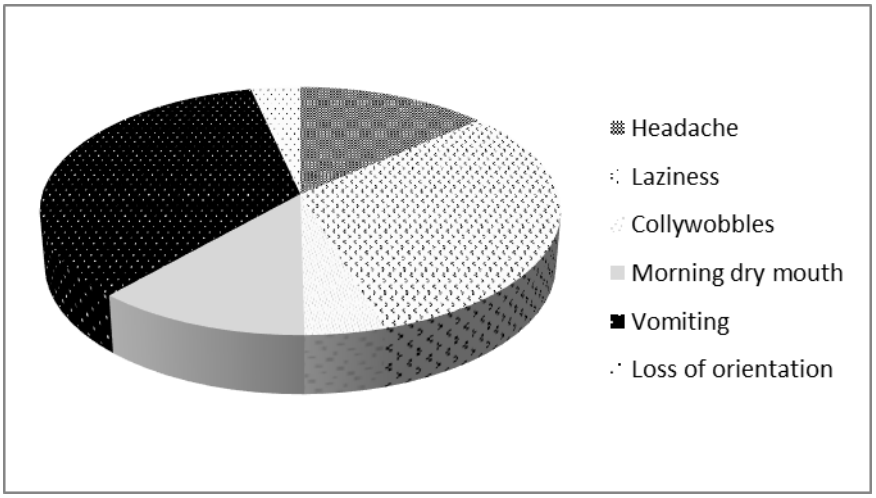


Figure No. 3
Main side effects informed by the Cuban population that consumes extracts of *P. neochillus* with medicinal purposes

To all of the 551 interviewees that referred to consume at least in an occasion this combined treatment, was also asked the reason why; receiving in 507 occasions the answer: to intensify the activity of the synthetic medication. The ways in which the interviewees answer this question reveal statistical differences according to the Chi-Square test for independent samples, pointing to the central region of the island like that with bigger frequency attending this practice of concomitant consumption of treatments to achieve bigger threshold of pharmacologic activity.

In the Table No. 2 appear the quantitative variables associated to the most significant uses and the total reports informed by the Cuban´s population. The higher value of IUV in the Eastern region is associate to the higher number of uses reported by the interviewees of this geographical area. It is also this region in which the main activities reported reaches the higher values of UST. These results give evidences once again to the high level of use that Cuban population does of this plant, even when no previous international reports refers it with it main purpose: The activity on the Central Nervous System.There is only one reference that can be indirectly correlated to this activity and is the "*in vitro*" inhibition of the acetylcholinesterase (AChE) enzyme referred by Brito *et al*. (2018).

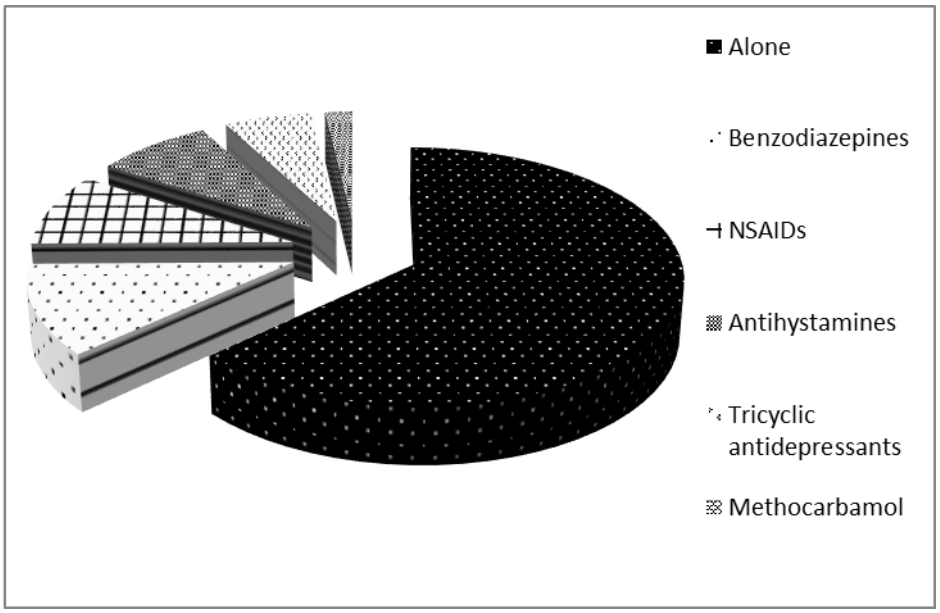


Figure No. 4
Drugs consumed concomitantly with extracts of *P neochillus* by the Cuban population

Table No. 2
Traditional uses, total of reports and quantitative ethno-botanic variables informed for *P. neochilus*by the Cuban population

REGIONS	WESTERN	CENTRAL	EASTERN
IVU	2.78	2.88	3.03
UST (%)	62.4 (Sedative) 54.4 (Hypnotic) 42.0 (Analgesic) 21.6 (Anti-inflammatory)	64.6 (Sedative) 57.0 (Hypnotic) 40.2 (Analgesic) 29.4 (Anti-inflammatory)	69.8 (Sedative) 59.0 (Hypnotic) 44.6 (Analgesic) 31.4 (Anti-inflammatory)

From the chemical point of view, some of the substances isolated from *P. nechillus* extracts refers the presence of triterpenes as friedelin, α and β-amyrinfattyacidesters; and flavonids (Viana, 2011), which had being tested to some that can be associate to some Central Nervous System diseases (Jeon *et al*., 2015).

CONCLUSIONS

*P. neochilus*Schltr is a plant specie recently informed as cultivated and consumed in Cuba because it sedative effects. Considering the results obtained it was demonstrated by the ethno-botanic study performed, that this plant is consumed alone or together with synthetic drugs (mainly benzodiazepines) to induce or enhance sedative or hypnotic effects by the Cuban population without no statistic differences between the three Cuban regions analyzed. The fact that this use is particularly specific by Cuba inhabitants, as reveal the bibliometric study, induce us to claim for new pharmacological experiments that should be developed in order to prove or to deny this large use by the Cuban Population. It is notified also some data that disclose the plant parts, concentration, preparation mode and other valuable information.

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