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Consumption of medicinal plants by the psychiatric population in Uruguay and their possible interactions with the most frequently prescribed medication

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ABSTRACT

The consumption of medicinal plants (MPs) has increased dramatically worldwide. In spite of the fact that they generally have a broad therapeutic range, they are not exempt of side effects and interactions when consumed concomitantly with conventional medication. The objective of this study was to analyze the consumption of medicinal plants by an Uruguayan psychiatric population in order to anticipate their possible interactions with the drugs commonly prescribed in these patients. Interviews of ambulatory patients who acquire their medications from the Pharmacy of Hospital Vilardebó were carried out. Evaluation of possible pharmacokinetic and pharmacodynamic interactions between twelve of the most prescribed conventional medications (quetiapine, lithium, flunitrazepam, sertraline, clonazepam, levomepromazine, haloperidol, valproic acid, olanzapine, fluoxetine, risperidone and clozapine) and the most consumed medicinal plants were studied. Two hundred and fifteen interviews were completed. 66% of the interviewed consumed medicinal plants. Potential interactions between the medication and the most consumed medicinal plants such as *Aloysia citriodora* (cedrón), *Achyrocline satureioides* (marcela), *Tilia platyphyllos* (tilo), *Baccharis trimera* (carqueja), *Mikania laevigata* (guaco) and *Matricaria chamomilla* (manzanilla) were found. A high consumption of medicinal plants was detected among these patients, thus enhancing the prevalence of their interactions with the studied drugs.

KEYWORDS: medicinal plants, psychiatric population, medicinal plant-drug interaction

INTRODUCTION

For centuries, before the arrival of scientific medicine, medicinal plants (MPs) were used by many cultures to treat a wide variety of ailments [1]. The pharmaceutical industry embraced this traditional knowledge and has used it to synthesize and elaborate medicines, which are commonly used in traditional Western treatments. The scientific verification process of this tradition is ongoing and new uses are discovered every day.

MPs are commonly defined as vegetal-origin products used to maintain or improve health. Although the estimation of sale rate is difficult to perform, the use of MPs concomitantly with conventional medicines is known to be not negligible [2]. However, this market is poorly regulated with regard to quality control and expenditure.

The natural origin of MPs may lead to a false impression about their safety [2], and this misconception results in their use among fragile population such as children, pregnant women and the elderly. Despite presenting a wide therapeutic range, MPs are no exempt of adverse effects and interactions; safety evaluation with regard to their

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toxicity and allergenic potential should be performed similar to that for conventional medicines and should be sustained, as far as possible, on a scientific basis [3]. Severe intoxications have been reported, especially associated with self-medication and lack of knowledge of the interaction of MPs with pathologies and conventional medication [4]. Information management is one of the main concerns regarding this topic. Most patients receive information from non-qualified interlocutors (friends and family) rather than from health professionals.

Phytovigilance consists in the supervision of side effects and drug interactions as a consequence of the use of herbal medicinal products, herbal food supplements, etc. Nowadays, phytovigilance is hardly conducted although it is mandatory in European countries [5]. Being a complex mixture of various bioactive products, MPs put researchers in a discouraging position because pharmacological actions depend on various phytochemicals with synergistic and antagonist actions taking place even in the same MP [4]. Therefore, the exact contribution of each active ingredient to the total activity, including possible interactions with conventional pharmacological treatments, is difficult to evaluate. What is more, the same MP harvested in different places or in different seasons may differ in composition, and thus in action. Additionally, not all individuals respond uniformly to a MP. Like conventional medication, factors such as genetics, sex, hepatic and renal function, co-morbidities, diet and age contribute to the heterogeneity of response [2].

Although guidelines exist on the manufacture of MP extracts, they are vague and do not deal with the fact that quality control of this kind of products is difficult to perform. Besides, in many regions of the world MPs are consumed as crude vegetable drugs and as a consequence have not undergone any quality control at all. As it is necessary that consumers have access to information and tools which enable adequate, safe and efficacious treatments, the World Health Organization (WHO) has published a new set of guidelines for national sanitary authorities for preparing context-specific reliable information regarding the use of alternative medicines [6]. Although guidelines cannot compensate for the low quality of some products or for inappropriate practices, they may help governments to educate consumers on how to obtain the maximum benefit of MPs and to reduce their risks to a minimum [6].

The knowledge that MPs may cause adverse events and interactions does not imply that its use should be totally discouraged, due to the fact that in some cases they are an adequate or even the only alternative to conventional medicine.

Polypharmacy has become a common clinical practice among psychiatric patients and up to one-third of patients visiting outpatient psychiatry department have been found to be on three or more psychotropic drugs [7-9]. The polypharmacy accompanied by the use of MPs presented by psychiatric patients, ingrained in our society, may place this kind of patients at higher risks of suffering from interactions of these MPs with conventional medication.

Vilardebó hospital, a 330-bed hospital, is the only acute psychiatric care center in Montevideo. It comes under the State Health Service Administration and it is integrated to the Public Health Network as a reference hospital for mental health problems.

The aim of this work was to perform a preliminary study to anticipate the possible interactions between the MPs mostly used by outpatients of Vilardebó Hospital and the most prescribed medicines in the center.

PATIENTS AND METHODS

Outpatients attending the pharmacy service for collection of the prescribed medication were selected randomly and interviewed during the period May-June 2016. A questionnaire was designed for this purpose that includes prescribed drugs, MPs consumed and their mode of preparation and reason for their use. The twelve most prescribed drugs among these patients were: quetiapine, lithium, flunitrazepam, sertraline, clonazepam, levomepromazine, haloperidol, valproic acid, olanzapine, fluoxetine, risperidone and clozapine. A bibliographical research was conducted in order to identify the relevant components of the plants consumed and the potential pharmacokinetic and pharmacodynamic interactions with the drugs aforementioned. Data collected was analyzed using Statistical Packages for Social Sciences (SPSS) version 17.

RESULTS

A total of 215 patients were interviewed. Sixty-six per cent of the interviewed patients (143) were using MPs. Among them 17% of the consumers admitted using two or more plants every day, 31% used one MP every day and the remaining 18% consumed MPs at least once during the studied period. The most consumed plant was *Aloysia citriodora* (cedrón), followed by *Achyrocline satureioides* (marcela), *Tilia platyphyllos* (tilo), *Baccharis trimera* (carqueja), *Mikania laevigata* (guaco) and *Matricaria chamomilla* (manzanilla) as shown in figure 1.

Ginkgo biloba and *Hypericum perforatum* were not among the most consumed plants; nevertheless, they were both part of a medicinal yerba which is used in the preparation of an infusion called mate that is widely used in our country.

As it can be observed in figure 2, infusion (tea and mate) was the most common way of preparation of the MPs.

DISCUSSION

Although 66% of those interviewed admitted the consumption of MPs, this figure is believed to be underestimated, probably because of the preconception that the use of MPs would not be approved by health professionals. Another fact that should raise concern is that the number and frequency of consumption of MPs among patients is high, which in turn contributes to a higher probability of presenting adverse events and/or interactions.

These results are in accordance with the international trend of increased use of MPs, backed up on the false perception of ample safety margin and harmlessness of natural products. This is reflected by the answers of most patients. Treating physician was seldom informed of the consumption of MPs. Also noteworthy is that some patients declared that they have been informed of the interactions and for this reason they discontinued the use of the MP. Some subjects fostered the use of MPs despite their physicians discouraging it. What is more, some patients admitted that they abandoned the therapy prescribed by the treating doctor, substituting it with natural therapy. On the other hand, some patients referred that they suffered from dizziness and hypotension after the use of a MP which resulted in its discontinuation, supporting the concept that consumption of MPs may entail risks.

Our country has deep traditional roots with regard to the use of MPs in infusions. The mode of preparation of such infusions does not differ from other Latin American countries.

Patients had, in general, good knowledge of the properties of each MPs consumed. *Aloysia citriodora* was mostly used because of its flavor but some

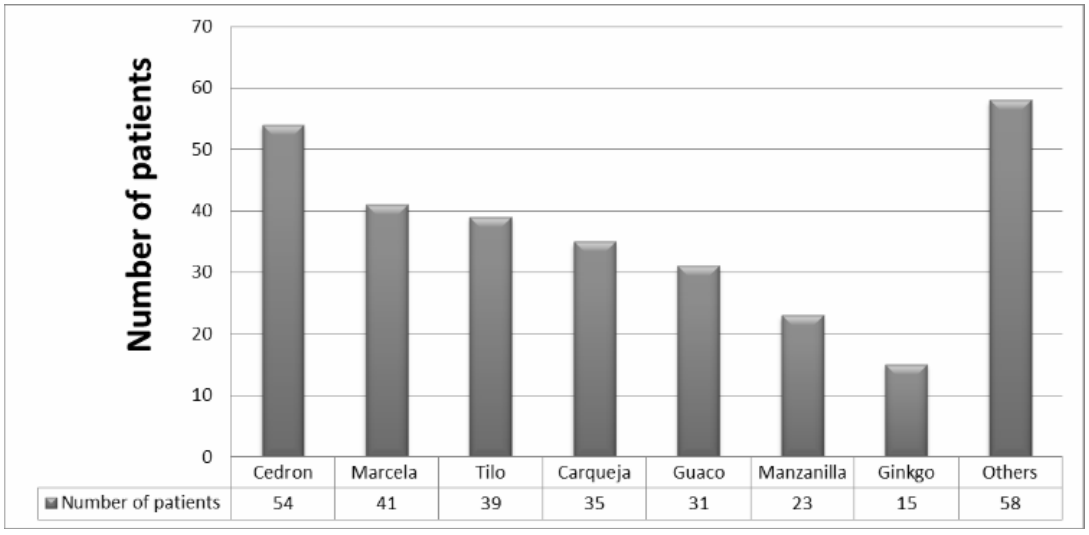

Figure 1. Most consumed medicinal plants.

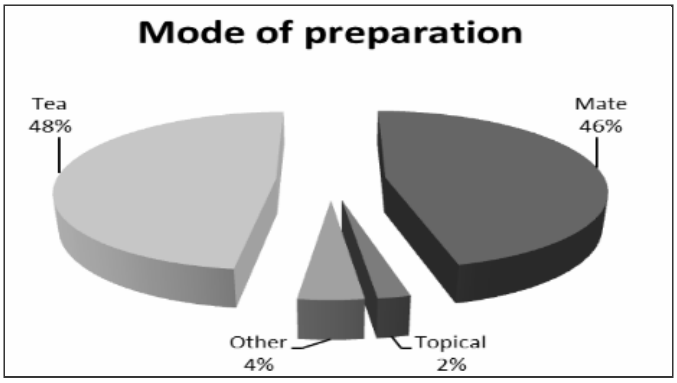

Figure 2. Mode of preparation of the medicinal plants consumed.

patients also pointed out that it has digestive properties and is beneficial to the heart. *Achyrocline satureioides* and *Baccharis trimera* were used because of their digestive properties. Hepatoprotective properties were also attributed to the latter. *Tilia platyphyllos* was used as a sedative, *Ginkgo biloba* for preventing memory deterioration, *Hypericum perforatum* as an antidepressant, *Mikania laevigata* was used to treat bronchitis, asthma and cough and *Matricaria chamomilla* was mainly used as a relaxing sleep aid and for its anti-inflammatory properties.

Pharmacodynamic and pharmacokinetic interactions have been reported for several components of the MPs studied. Limonene, which is present in two of the MPs studied, *Aloysia citriodora* and *Achyrocline satureioides* [10], has antidepressant effects producing an increase in neurotransmitters such as serotonin and dopamine in the brain [11, 12]. It has been shown that the dispersion of limonene in the air of a hospital setting improves depressive symptoms of inpatients [12]. Selective serotonin reuptake inhibitors (SSRIs) such as sertraline and fluoxetine produce an increase in serotonin in the synaptic cleft, which could be potentiated by the use of a MP that contains limonene. This synergistic effect could end up in a serotonin syndrome characterized by autonomous dysfunction, neuromuscular deterioration and mental status alterations [13]. Another factor that should be taken into account is the possibility of suffering from coagulation disturbances due to the inhibition of serotonin reuptake in platelets [14, 15]. Taking into consideration that SSRIs were one of the drug classes mostly prescribed and that, as it was mentioned before, serotonin participates in platelet aggregation, the effect *Ginkgo biloba* exerts on coagulation, inhibiting platelet activation factor (PAF) [16] and thereby placing patients at higher risks of coagulation disorders should not be disregarded. *Mikania laevigata* and *Matricaria chamomilla* are rich in coumarin content [17, 18]. Coumarin has an anti-coagulant and blood thinning effect and hence increased bleeding risk with concurrent use of SSRIs and *Mikania laevigata* and *Matricaria chamomilla* may be present [19].

When used concomitantly with antipsychotics, such as risperidone, quetiapine, levomepromazine, olanzapine, clozapine and haloperidol, *Aloysia citriodora* and *Achyrocline satureioides* may show lesser efficacy due to the increase in serotonin and dopamine levels both plants produce.

Hyperforin has been recently shown to be a major antidepressant component in the extract of *Hypericum perforatum* also known as St John's Wort. It inhibits, like conventional antidepressants, the neuronal uptake of serotonin and dopamine. This may synergize fluoxetin and sertraline mechanism of action [20-23].

Linalool, one of the components of *Aloysia citriodora,* has inhibitory properties over glutamate activity, thus exerting anticonvulsant activity. The modulation of glutamate activity also confers sedative and anxiolytic properties to linalool. These effects may synergize with the action of valproic acid [24-26] and benodiazepines.

Tilia platyphyllos also has sedative properties, which may enhance the depressor effects of anxiolytics and hypnotics on central nervous system (CNS). This effect may be connected to a flavonoid called

Table 1. Potential interactions between medicinal plants and the drugs studied.

Drug	Medicinal plants	Interactions
Clonazepam, Flunitrazepam	*Tilia platyphyllos* *Matricaria chamomilla*	Potentiate sedative effect over CNS
	Aloysia citriodora *Achyrocline satureioides*	Increase concentration due to metabolism inhibition
	Hypericum perforatum *Ginkgo Biloba*	Decrease concentration due to metabolism induction
Quetiapine, Levomepromazine	*Achyrocline satureioides* *Aloysia citriodora*	Increase concentration by inhibition of metabolism or decrease efficacy due to antagonism of effects
	Hypericum perforatum	Decrease concentration due to metabolism induction
Risperidone	*Achyrocline satureioides* *Aloysia citriodora*	Decrease efficacy due to antagonism of effects and increase concentration by inhibition of metabolism
	Hypericum perforatum	Decrease concentration due to metabolism induction
	Ginkgo Biloba	Increase concentration due to metabolism inhibition
Haloperidol, Clozapine, Olanzapine	*Achyrocline satureioides* *Aloysia citriodora*	Increase concentration by inhibition of metabolism or decrease efficacy due to antagonism of effects
	Hypericum perforatum	Decrease concentration due to metabolism induction
	Matricaria chamomilla	Increase concentration due to metabolism inhibition
	Ginkgo Biloba	Increase concentration due to metabolism inhibition
Fluoxetine, Sertraline	*Achyrocline satureioides* *Aloysia citriodora*	Synergism of effects
	Hypericum perforatum	Synergism of effects (higher incidence) or decrease concentration due to metabolism induction
	Mikania laevigata *Matricaria chamomilla*	Increase risk of bleeding
	Ginkgo Biloba	Increase concentration due to metabolism inhibition, Higher risk of bleeding
Lithium	*Tilia platyphyllos* *Baccharis trímera*	Increase concentration due to decreased renal excretion
Valproic acid	*Aloysia citriodora*	Synergism of anticonvulsant effects

kaempferol, which exhibits gamma amino butyric acid (GABA) agonist properties, similar to benzodiazepines such as clonazepam and flunitrazepam [27, 28]. *Matricaria chamomilla* was also found to exert anxiolytic effect [29].

Flavonoids such as quercetin and scoparone (furanocoumarins), which are components of *Aloysia citriodora* and *Achyrocline satureioides* are inhibitors of CYP1A2 and CYP3A4 isoenzymes [30-33]. *Achyrocline satureioides* has another constituent

called luteolin which is an inhibitor of CYP3A4 [34]. Clozapine, haloperidol and olanzapine are substrates of CYP1A2 whereas quetiapine, flunitrazepam, levomepromazine, clonazepam, haloperidol, clozapine and risperidone are substrates of CYP3A4 isoenzyme. As a result, *Aloysia citriodora* and *Achyrocline satureioides* have offsetting effects over quetiapine, olanzapine, haloperidol, clozapine, risperidone and levomepromazine. On the one hand these plants increase serotonin and dopamine levels antagonizing the effects of antipsychotic drugs but on the other hand they inhibit the metabolism of these drugs, increasing their blood concentration. The final outcome of these interactions is difficult to predict and will depend on the prevailing mechanism [35, 36].

Gingko biloba as well as *Hypericum perforatum* have components that inhibit or induce some isoenzymes of the cytochrome CYP450 system, thus interfering with the metabolism of several drugs. *Gingko biloba* has a biphasic activity over CYP2D6 (inhibitor at lower concentrations and inducer at higher ones) [37]. This isoenzyme is involved in the metabolism of clozapine, olanzapine, haloperidol, fluoxetine, sertraline and risperidone. *Gingko biloba* also inhibits CYP1A2 whose substrates were mentioned before. On the contrary, it induces CYP2C19 [38], responsible for flunitrazepam and clonazepam metabolism. *Hypericum perforatum* induces the activity of CYP1A2 and CYP3A4 [39, 40]. These two MPs as well as others containing quercetin interfere with the activity of P-glycoprotein (P-gp) [41, 42], efflux transporter that is present in diverse areas of the organism such as the gastrointestinal tract, myocardium and blood brain barrier. The modulation of P-gp activity and expression by these herb constituents may result in altered absorption and bioavailability of drugs such as clozapine that are Pgp substrates [2, 43, 44]. The activity of CYP1A2 is sensitive to inhibition by *Matricaria chamomilla*. *Chamomile* is only a weak inhibitor of CYP2C9 [45].

Diuretics increase lithium plasma levels up to 50% by depleting sodium. *Tilia platyphyllos* and *Baccharis trimera* exhibit diuretic properties [46, 47] leading to potentially toxic serum levels of lithium [48].

Table 1 summarizes the potential interactions between MPs and the drugs studied.

Compared to treatments with conventional medication, the amount of information about the relative safety of herbal remedies is limited. Little documentation exists on the long term toxicity of herbs. There is no use of standard/measured doses, and the large volumes of the doses used are difficult to manage. Moreover, there is lack of communication between patients and physicians on the consumption of MPs. On the one hand, patients believe that MPs do not interfere with conventional medicines and comorbidities, and on the other, health care professionals seldom include the use of MPs in the questionnaire performed during medical consultation. What is more, health professionals are rarely aware of the properties of MPs and their possible effects and/or interactions.

CONCLUSION

Our results are in accordance with the international trends of increasing MPs used in the population. Although this preliminary study was based mostly on bibliographical research, it has shed light on multiple potential interactions between MPs and conventional medication.

It is necessary to understand the importance of reporting the consumption of MPs and to foster the communication between patients and health care professionals. Safety studies endorsed by health professionals may promote the rational use of MPs through education and regulation, maximizing their benefits and avoiding unnecessary risks.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

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