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Federal University of Rio de Janeiro State



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## RESEARCH

### Potenciais interações relacionadas ao uso de medicamentos, plantas medicinais e fitoterápicos em mulheres no período do climatério

Potential drug interactions in relation with the use, medicine plants and herbal in premenopausal women period

Potenciales interacciones de la droga con el uso, plantas medicinales y hierbas en las mujeres en periodo premenopáusicas

Gabriela Tassotti Gelatti <sup>1</sup>, Karla Renata de Oliveira <sup>2</sup>, Christiane de Fátima Colet <sup>3</sup>

#### ABSTRACT

**Objective:** To identify the potential interactions resulting from the use of medicinal plants and herbal concomitant with medicine used by menopausal women. **Method:** This was a cross-sectional, descriptive and analytical study of 87 climacteric women receiving care at Family Health Strategies VII and VIII of the city of Ijuí/RS and that are part of institutional research "Multidimensional study of women in the aging process". **Results:** Of the 87 women studied, 55 used at least one medicinal plant and nine women used at least one concomitant herbal medicinal products, a total of 26 women exposed to interactions between plants and medicines and six women exposed to interactions between herbal medicines and medicines. **Conclusion:** The study revealed high exposure to interactions resulting from the use of medicinal plants and herbal with medicines in the users of the Unit Health System in the city and the monitoring of the use of these products by health professionals is necessary. **Descriptors:** Climacteric, Herbal medicine, Medicinal plants, Drug interactions, Family health strategy.

#### RESUMO

**Objetivo:** Identificar as potenciais interações decorrentes do uso de plantas medicinais e fitoterápicos concomitante a medicamentos utilizados por mulheres climatéricas. **Método:** Trata-se de um estudo transversal, descritivo e analítico realizado com 87 mulheres climatéricas atendidas nas Estratégias de Saúde da Família VII e VIII do município de Ijuí/RS, e que fazem parte da pesquisa institucional "Estudo multidimensional de mulheres no processo de envelhecimento". **Resultados:** Das 87 mulheres estudadas, 55 utilizavam pelo menos uma planta medicinal e nove mulheres utilizavam pelo menos um fitoterápico concomitante a medicamentos, totalizando 26 mulheres expostas a interações entre plantas e medicamentos e seis mulheres expostas a interações entre fitoterápicos e medicamentos. **Conclusão:** O estudo revelou alta exposição a interações decorrentes do uso de plantas medicinais e fitoterápicos concomitante a medicamentos em usuárias do Sistema Único de Saúde municipal, mostrando-se necessário o acompanhamento do uso desses produtos pelos profissionais de saúde. **Descritores:** Climatério, Fitoterapia, Plantas medicinais, Interações de medicamentos, Estratégia de saúde da família.

#### RESUMEN

**Objetivo:** Identificar las interacciones potenciales que pudieran resultar del uso de plantas medicinales y fármaco concomitante a base de hierbas utilizados por las mujeres menopáusicas. **Método:** Se realizó un estudio transversal, descriptivo y analítico de 87 mujeres climatéricas que reciben atención en salud de la familia Estrategias VII y VIII del municipio de Ijuí/RS y que son parte de la investigación institucional "Estudio multidimensional de las mujeres en el proceso de envejecimiento". **Resultados:** De las 87 mujeres estudiadas, 55 utilizaron al menos una planta medicinal y nueve mujeres utilizan al menos uno de los medicamentos a base de hierbas concomitantes, un total de 26 mujeres expuestas a las interacciones entre plantas y medicinas y seis mujeres expuestas a las interacciones entre los medicamentos a base de hierbas y medicinas. **Conclusión:** El estudio reveló una alta exposición a las interacciones que resultan del uso de plantas medicinales y fármaco concomitante de hierbas en los usuarios del sistema único de salud municipal y el seguimiento de la utilización de estos productos por los profesionales de la salud es necesario. **Descritores:** Climaterio, Medicina natural, Plantas medicinales, Interacciones medicamentosas, Estrategia de salud para la familia.

1 Pharmacist, Master's Student of the Postgraduation Program Stricto Sensu in Integral Attention to Health - Unicruz/Unijui. E-mail: gabriela.gelatti@hotmail.com 2 Pharmacist, Master of Biological Sciences: Biochemist, Federal University of Rio Grande do Sul. E-mail: karla@unijui.edu.br 3 Pharmacist, Master in Pharmaceutical Sciences from the Federal University of Rio Grande do Sul. E-mail: chriscolet@yahoo.com.br

## INTRODUCTION

**C**onsumption of medicinal plants and herbal medicines has increased worldwide over the years, and this growth is related to several factors, among which stand out the disappointment with the results obtained in conventional treatments; undesirable effects and damage caused by abuse and/or misuse of medicines; difficulties of access to medicines and even the popular belief that natural products are harmless.<sup>1</sup> According to Veiga Jr. et al.<sup>2</sup> the population of the poorest countries make use of medicinal plants by tradition and the absence of viable economic alternatives, while in developed countries there has been increased use of phyto influenced by fads that stimulate the consumption of natural products.

Brazilians are also increasingly interested in treatments "safe" and "natural" to promote a healthier life. In Brazil, about 82% of the population use products based on medicinal plants,<sup>3</sup> of which the use is higher for women, and the use of drugs. This data can be justified from the feminine behavior, given that women have a greater concern for health, are more attentive to symptoms of disease and seek more health services than men.<sup>4-5-6</sup> Specifically, during menopause, many women experience vasomotor, neuropsychiatric symptoms and sexual dysfunction. Still, the effects of hormonal changes may increase the incidence of hypertension, cardiovascular disease, osteoporosis, hypothyroidism, obesity, diabetes mellitus and psychosocial disorders. In many cases, treatment for these clinical manifestations drugs are used, increasing in this age range to medicate.<sup>7</sup>

For many patients, the use of a single drug is not enough, and when two or more medicines are prescribed, not always the desired benefit is achieved, since they can interact negatively, which may increase or diminish the therapeutic effect or toxic effect of one or the other.<sup>8-9</sup> It should be noted that these interactions are not restricted to the world of synthesized chemicals, but can occur among those present in plants that are used as teas, syrups and herbal.<sup>10</sup>

It is noteworthy that the risk of the occurrence of interactions involving medicinal plants and herbal medicines may be greater than the interactions between medicines, as these usually contain unique chemicals, while almost all plants (even products containing only a plant) containing mixtures of substances pharmacologically active, increasing the possibility of interactions occur.<sup>11-12</sup>

Thus, this study aims to identify the potential interactions resulting from the use of medicinal plants and herbal concomitant drug used by women in the climacteric period.

## METHOD

It is a study of cross-sectional descriptive and analytical type. The sample consisted of 87 climacteric women attending the Family Health Strategy (FHS) VII and VIII of the municipality of Ijuí/RS and that are part of institutional research called "multidimensional study of women in the aging process" approved by the Ethics Committee Regional Research at the University of the State of Rio Grande do Sul Northwest (UNIJUÍ) under the Embodied Opinion nº 864.988.

Data were collected by applying a questionnaire at the residence of the participants after the signing of the Informed Consent and, from December 2013 to February 2014.

The variables of interest for data collection were: sociodemographic characteristics, use of medicinal plants, herbal and medicine. To identify and herbal medicines has asked the respondent to submit the used of each product box and failing, prescription in use. Among the cited plants, those that have provided interviewed were collected and identified as the species and/or botanical family, by an agronomist. The samples contained parts like leaves, flowers and fruits, giving priority to adult branches. Those that were not available at the time of the interview, was considered the self-report.

We used the concepts described in Herbal form of the Brazilian Pharmacopoeia<sup>29</sup> which defines:

a) Medicinal plant - plant species, cultivated or not, used for therapeutic purposes; b) Phytotherapeutic - the product of medicinal plant or its derivatives, except single substances with prophylactic purpose, curative or palliative; c) Drug - pharmaceutical product, technically obtained or prepared, containing one or more drugs and other substances with prophylactic, curative, palliative or diagnostic purposes, where they are established the prescriber-pharmacist-user relationship.

The drugs were classified according to first and second levels of the Anatomical Therapeutic Chemical Code (ATC).<sup>13</sup> To identify and classify the interactions arising from the use of concomitant medicinal plants and herbal medicines have been used in the Micromedex®<sup>14</sup> and Medscape,<sup>15</sup> databases website drugs.com,<sup>16</sup> beyond books: DRUG INTERACTIONS OF STOCKLEY<sup>17</sup> and ADVERSE DRUG INTERACTIONS.<sup>18</sup> When the same interaction found in books and databases, data was prioritized basis. To identify interactions, were excluded herbal with more than one active component.



Interactions were classified according to the severity according to the website drugs.com<sup>16</sup> and databases Micromedex<sup>14</sup> and Medscape<sup>15</sup> and the latter not conceptualizes the smallest interactions:

- a) Higher/series - combinations should be avoided because the risk outweighs the benefit of interaction;<sup>16</sup> may have life-threatening and require medical intervention to reduce or avoid serious adverse effects;<sup>14</sup> must use other alternatives.<sup>15</sup>
- b) Moderate/significant - should generally avoid combinations and use them only in special circumstances;<sup>16</sup> may result in worsening of the clinical condition of the patient, requiring modification of the established drug therapy;<sup>14</sup> should monitor the use.<sup>15</sup>
- c) Minor - should assess the risk and consider an alternative medication, take steps to circumvent the risk of interaction and/or institute a monitoring plan;<sup>16</sup> when the patient change in clinical status, but does not require modification of drug therapy.<sup>14</sup>

Also considered were the concepts presented in the book of DRUG INTERACTIONS OF STOCKLEY<sup>17</sup> that classifies interactions: interactions in which there is an outcome that threatens the life, in this case is considered better to avoid the simultaneous use; interactions where simultaneous use can result in significant risk to the patient, requiring dosage adjustment and rigorous monitoring; interactions where there is a potentially dangerous outcome, but how data is scarce, the findings on the interaction are difficult to draw; There is doubt about the result of concurrent use, and therefore you may need to educate patients about possible adverse effects and/or consider monitoring; and interactions that are not considered clinically important. The book ADVERSE DRUG INTERACTIONS<sup>18</sup> do not classify the interactions as the severity.

In cases of disagreement between the data bases, as regards the interaction classification, the most serious was adopted.

To analyze the data we used the Statistical Package for Social Sciences (SPSS). For categorical variables we used absolute and relative frequency, and quantitative variables, mean and standard deviation. It was performed Student t test for independent samples to compare the means of variables: number of medicinal plants used x number of drugs used. It was considered significant at  $p < 0,05$ .

This study is a subproject linked to institutional research mentioned above and was approved by the Research Ethics Committee of UNIJUÍ Embodied under Opinion nº 524.871.

## RESULTS AND DISCUSSION

The 87 study participants had a mean age of  $51,5 \pm 8,4$  years, with a minimum of 34 and maximum of 69 years. Regarding marital status, 49 (56,98%) are married, among women with their own income, 37 (43,02%) reported receiving one to two minimum salaries. As for education, it was found that 38 (44,19%) women did not complete primary school.

The use of medicinal plants was reported by 82 (94,3%) respondents, averaging  $4,24 \pm 2,89$  plants per woman. The majority (79,27%) mentioned knowing the use of medicinal plants for traditional indications, transmitted from generation to generation. Among the plants acquire sites, 46 (56,09%) reported cultivate in their homes. In each use, 59 (71,95%) women were using a single type of medicinal plant and 23 (28,05%) used mixtures. Were cited 82 different species of medicinal plants, and the most used were *Matricaria recutita* (chamomile) (n=40), *Achyrocline satureioides* (Marcela) (n=38), *Cymbopogon citratus* (lemon) (n=25), *Plectranthus barbatus* (false Boldo) (n=24) and *Mentha x piperita* (Mint) (n=17).

The high use of medicinal plants was also observed in Teutonic/RS, one practice among 92,9% of respondents, with an average of  $4,8 \pm 3,7$  plants/person. Other data similar to the present study were observed: 74,8% of respondents mentioned knowing the use of medicinal plants through relatives, and also 58,6% of the plants mentioned are grown in the residence of respondents.<sup>19</sup> Whereas the municipality Teutonic is located in central and Ijuí in the northwest of the Rio Grande do Sul (RS), one can infer that the high use of medicinal plants is a state characteristic. But in other regions of Brazil the reality is similar, whereas in Uberlandia/MG and Sao Paulo/SP was found that 76,7% and 68% of respondents, respectively, reported using some medicinal plant.<sup>20-21</sup>

The World Health Organization (WHO) has encouraged the use of complementary therapies in health systems. In this sense, Brazil, in 2006, the Ministry of Health approved the National Policy on Integrative and Complementary Practices in the Unified Health System (SUS) (PNPIC)<sup>22</sup> and the National Policy on Medicinal Plants and Herbal Medicines (PNPMF)<sup>23</sup> including in its guidelines to promote the rational use of medicinal plants and herbal medicines in SUS. Most experiments on the public network is based on the Living Pharmacy model,<sup>24</sup> established by the Ministry of Health through Ordinance No. 886, of April 20, 2010.<sup>25</sup> Other advances are noteworthy, such as the publication of the National List of Medicinal Plants interest to the SUS (RENISUS);<sup>26</sup> publication of RDC No. 10/2010,<sup>27</sup> in the Annex I lists 66 species of medicinal plants, as well as information for their use; preparation of Herbal form of the Brazilian Pharmacopoeia;<sup>28</sup> include eight herbal cast in the National List of Essential Medicines (RENAME);<sup>29</sup> Instruction No. 2/201430 which brings

a list of 27 authorized herbal medicines and traditional herbal 16 products with information for their use; besides the approval of policies and state and local programs and investments in structuring programs/projects phytotherapy in SUS. Please note that the RS state recently approved a State Policy on Integrative and Complementary Practices (EPCIP/RS), through Resolution 695/2013 CIB,<sup>31</sup> which includes various therapeutic activities, including the implementation of herbal and medicinal plants in the SUS.

The use of herbal medicines was reported by 13 (14,9%) respondents, averaging 1,38±0,87 for herbal woman being cited 12 different herbal medicines. The most *Ginkgo biloba* has been used (n=7) (Table 1).

Table 1 - Distribution of herbal remedies cited by women registered in the FHSs according to VII and VIII, according to autorreferida and frequency of service indication. Ijuí/RS, 2013-2014.

Phytotherapeutic	Statement reported by the interviewee	Frequency of service N (%)
<i>Ginkgo biloba</i> (ginkgo) 80mg	Memory, circulation, regulation of Ear pressure	7 (58,33%)
<i>Cynara scolymus</i> (artichoke) 500mg	Weight reduction	1 (8,33%)
<i>Aesculus hippocastanum</i> (horse chestnut) 100mg	Varicose veins	1 (8,33%)
<i>Borago officinalis</i> (gamaline) 900mg	Breast pain	1 (8,33%)
<i>Paullinia cupana</i> (guarana) 500mg	Refreshing	1 (8,33%)
<i>Glycine max</i> (isoflavone) 50mg	Hot flashes	1 (8,33%)
<i>Linum usitatissimum</i> (Flaxseed)	Weight reduction	1 (8,33%)
Compound with 37 herbs*	Weight reduction	1 (8,33%)
Compound "Multimix"*	Weight reduction	1 (8,33%)
Compound with 3 herbs*	Weight reduction	1 (8,33%)
Compound "drought belly"*	Weight reduction	1 (8,33%)
<i>Uncaria tomentosa</i> (catclaw acacia) 100mg	Joint pain	1 (8,33%)

OBS: All herbal included in this table were used by respondents in the pharmaceutical capsule form. \* It was not considered for the identification of interactions.

Studies have shown a preference for medicinal plants of the population,<sup>19-20</sup> on the other hand, herbal that are obtained with exclusive use of vegetable raw materials which are safe and effective based on clinical evidence and are characterized by their quality constancy,<sup>32</sup> They do not have the same credibility as medicinal plants. In this study, we found that few women used herbal, probably because they are not considered by them, without risk just as medicinal plants, or the high frequency of home cultivation of plants for consumption by the interviewees, and present a lower cost compared to herbal.

In Uberlandia/MG, the use of herbal medicines was reported by 5,5% of respondents, and *Ginkgo biloba* the most widely used herbal medicine,<sup>20</sup> similar to this study. *Ginkgo biloba* is among the herbal recognized by the Ministry of Health, is indicated for dizziness and tinnitus (tinnitus) resulting from circulatory disorders, peripheral circulatory disorders (intermittent claudication) and cerebral vascular insufficiency,<sup>30</sup> also is used to improve cognitive function in cases of dementia and memory loss<sup>17</sup>, is in conformity with the indications reported by women in the study. It is noteworthy that in this study the *Ginkgo biloba* herbal medicine was the most involved in interactions, probably because it was mostly used by women, as has been widely reported by the media and the fact that the plant affects various cytochromes P450. Another fact that may explain the higher frequency of interactions related to herbal medicine that is related to its ancient use and the numerous queries related to this product.

In a study conducted in Maracanau/EC, the Family Health Units of users, of which 85,4% were women with an average age of 36,93±15,9, it was found prevalence of 20,6% of herbal medicines in prescriptions, possibly due to the municipality develop Vivas Pharmacies program in the public health system,<sup>4</sup> which is not the reality of the studied FHSs.

When women were asked of being informed by the doctor about the use of medicinal plants and herbal medicines, the majority (57,32%) said no report, which was also observed by Machado et al.<sup>20</sup> It should be noted that the prescriber of ignorance level on the use increases the risk to the user, especially when with plants and concomitant herbal drug self-medication is carried and can have the effect of synergistic effects or lack of effect, and those not covered by doctor.<sup>33</sup> in relation to situations in which concomitant use of the products under study resulting in reduced effect of some drug used, as noted in Tables 2 and 3, can induce the physician to prescribe an unnecessary drug and further worsen the health condition patients lack the desired effect. On the other hand, if the doctor is informed about the use of plants and/or herbal, study Da Rosa et al.<sup>34</sup> shows a lack of knowledge of these professionals about this therapy, which can cause them to disregard the patient's report on the Use of plant and/or herbal medicines.

On the use of drugs, 59 (67,82%) respondents said they use at least one, averaging 3,37±2,71 per woman, totaling 76 different medications. No statistically significant difference was observed ( $p=0,05$ ) between the number of medicinal plants and the number of medications used by women. The most commonly used, according to the ATC,<sup>13</sup>



act on the nervous system (30,6%), which may be related to the fact that this classification include analgesics, which are often used by self-medication. In addition, this group includes anxiolytics and antidepressants that were also cited by respondents. The second highest rate was for medicines for diseases of the cardiovascular system, suggesting the presence of hypertensive women, given the high prevalence of the disease in the general population. These data are similar to the study of Teutonic/RS, with a population with an average age of 44,4±13,9 years, 87,2% women, in which the most commonly used medications act on the nervous system (25,7%), followed by acting on the cardiovascular system (18,4%).<sup>19</sup>

No respondent reported discontinue use of plant and/or herbal when used concurrently to any medicine by the manifestation of side effects, which can be explained by lack of knowledge about the risk associated with concomitant use of plants and herbal medicines with medications, or assign the adverse effect occurred to the drug, mainly because most of the respondents (77,01%) reported that plants and/or concomitant herbal medicinal products carry no health risks and the majority reported that they may complement the action of the drug.

In a study conducted in the north central region of the state of Rio de Janeiro, 47,5% of respondents reported that medicinal plants are used together with drugs, whenever know a plant that may be indicated for the treatment they need.<sup>33</sup> In the present study, we found higher results in relation to such conduct, increasing the risk of interactions, as of 59 women who used drugs, 55 (93,22%) used at least one medicinal plant and a drug concomitantly a total of 26 (47,27%) women exposed to interactions between plants and medicines, eight (30,77%) are exposed to more than one interaction. 34 were identified potential interactions, averaging 1,85 interactions per woman.

Among the plants used by the interviewees, which may interact with medications used for them, it was found that the *Camellia sinensis* (black/green tea) and *Pyros Malus* (Apple) are not recognized therapeutic use by the Ministry of Health, as are not in national relationships published to date.<sup>26-27-28-29-30</sup> Please note that most interactions involve chronic drug use, which exposes women to interactions for long periods. It is mainly for this reason that it is necessary to inform the doctor about the use of medicinal plants and which plants used concomitantly with medications because with this information the doctor can opt for medicines that do not interact with the plants used or can replace tea to avoid interactions with medicines used.

As the severity of the interactions has been found in the data bases 11 (32,35%) are lower risk, 14 (41,18%) had moderate/significant three (8,82%) larger/serious. It was found that for three (8,82%) interactions there is doubt about the result of the simultaneous use, one (2,95%) presents significant risk to the patient<sup>17</sup> and about two (5,88%) interactions were not found to severity<sup>18</sup> reports (Table 2).

It was observed that the three potential interactions between herbal and major/serious severity of medicines involving *Hypericum perforatum* (St. John's wort), indicated for the treatment of mild to moderate depression, seasonal affective disorders, bad

mood, anxiety and insomnia, particularly if associated with menopause<sup>17</sup> In addition to the plant in nature, are available in the herbal market containing this plant, which could be prescribed by doctors with guidelines on the use, and most likely to achieve the correct dose, which is not guaranteed with the plant, since the also influenced the method of preparation of tea and lack of standardization. Evidence suggests that it exerts a biphasic effect on several cytochromes P450, with inhibitions observed in in vitro studies with an initial exposure and induction resulting from long-term use. In the case of the interaction of *Hypericum perforatum* with estradiol, prednisone, and carbamazepine, the three largest potential/serious interactions observed in this study, there is induction of CYP3A4 activity, thus reducing the serum levels and effects of said drugs, and the output appears vary in accordance with the present hyperforin content in the plant.<sup>17</sup>

Table 2 presents the potential interactions between herbal medicines and identified in menopausal women enrolled in FHSs VII and VIII.

Table 2 - Potential interactions between herbs and drugs identified in weather women registered in the FHSs VII and VIII. Ijuí/RS, 2013-2014.

Medicinal plant	Medication	Effect	Severity	N (%)
<i>Plectranthus barbatus</i> (false Bilberry)	Ibuprofen <sup>15</sup>	↑ risk for bleeding	Moderate/significant	2 (4,17%)
	Propranolol <sup>15</sup>	↑ effect of propranolol	Minor	2 (4,17%)
	Metformin <sup>15</sup>	stimulation of insulin liberation	Minor	1 (2,08%)
	Ketoprofen <sup>15</sup>	↑ risk of bleeding	Moderate/significant	1 (2,08%)
	Drospirenone <sup>15</sup>	↑ effect of drospirenone	Minor	1 (2,08%)
	Hydrochlorothiazide <sup>15</sup>	↑ effect of hydrochlorothiazide	Minor	1 (2,08%)
<i>Hypericum perforatum</i> (St. John's wort)	Estradiol <sup>14-15-16-17-18</sup>	↓ effect of estradiol	Greater/Serious	1 (2,08%)
	Clonazepam <sup>14</sup>	↓ effect of clonazepam	Moderate/significant	1 (2,08%)
	Cafein (Neosaldina) <sup>17</sup>	↑ metabolism of cafein	Minor	1 (2,08%)
	Prednisone <sup>15,17</sup>	↓ effect of prednisone	Greater/Serious	1 (2,08%)
	Carbamazepine <sup>14-15-16-17</sup>	↓ effect of carbamazepina	Greater/Serious	1 (2,08%)
	Alprazolam <sup>14-15-16-17</sup>	↓ effect of	Moderate/	1 (2,08%)

		alprazolam	significant	
<i>Eucalyptus globulus</i> (eucaliptus)	Clonazepam <sup>15</sup>	↑ sedation	Minor	1 (2,08%)
	Estradiol <sup>15</sup>	↓ effect of estradiol	Moderate/significant	1 (2,08%)
	Alprazolam <sup>15</sup>	↑ sedation, ↓ effect of alprazolam	Moderate/significant	1 (2,08%)
<i>Salvia officinalis</i> (sage)	Codein <sup>15</sup>	↑ sedation	Minor	1 (2,08%)
	Metphormine <sup>15</sup>	↑ effect of metphormine	Minor	1 (2,08%)
<i>Matricaria recutita</i> (chamomile)	Acetylsalicylic acid (AAS) <sup>15,18</sup>	↓ effect of chamomile, ↑ risk of bleeding	Moderate/significant	4 (8,32%)
	Prednisone <sup>15</sup>	↓ effect of chamomile	Minor	2 (4,17%)
	Ketoprofen <sup>15</sup>	↓ effect of chamomile, ↑ risk of bleeding	Moderate/significant	1 (2,08%)
	Clopidogrel <sup>18</sup>	↑ risk of bleeding	Not found	1 (2,08%)
	Clonazepam <sup>18</sup>	↑ sedation ↓ effect of	Not found	1 (2,08%)
	Ibuprofen <sup>15</sup>	chamomile, ↑ risk of bleeding	Moderate/significant	1 (2,08%)
	Diclofenaco <sup>15</sup>	↑ risk of bleeding	Moderate/significant	1 (2,08%)
<i>Camellia sinensis</i> (black tea/green)	Enalapril <sup>17</sup>	↑ moderate in blood pressure	There is doubt about the use of simultaneous use	3 (6,25%)
	Hidroclorotiazida <sup>17</sup>	↑ moderate in blood pressure	There is doubt about the use of simultaneous use	2 (4,17%)
	Fluoxetina <sup>15</sup>	↑ risk of bleeding	Moderate/significant	2 (4,17%)

	Ibuprofen <sup>15</sup>	↑ risk of bleeding	Moderate/significant	1 (2,08%)
	Litium <sup>15,18</sup>	↑ levels of litium	Minor	1 (2,08%)
<i>Cinnamomum verum</i> (cinnamon)	Ibuprofeno <sup>15</sup>	↑ risk of bleeding	Moderate/significant	1 (2,08%)
<i>Pyrus malus</i> (apple)	Hydrochlorothiazide <sup>15</sup>	hypokalemia	Minor	1 (2,08%)
<i>Pimpinela anisum</i> (fennel)	Estradiol <sup>17</sup>	active constituents of fennel seem shows estrogenic activity	There is doubt about the result of the simultaneous use	3 (6,25%)
	Diclofenaco <sup>15</sup>	↑ risk of bleeding	Moderate/significant	1 (2,08%)
<i>Mentha x piperita</i> (mint)	Omeprazol <sup>17</sup>	↓ effect of omeprazol	Significant risk to the patient	3 (6,25%)
Total	34	-	-	48 (100%)

The most frequent interaction was observed *Matricaria recutita* (chamomile) with AAS, as four women are exposed. These may incur to reduce the effects of *Matricaria recutita*,<sup>15</sup> and it can increase the risk of bleeding because the cumarin present in the plant exert discreet anticoagulant effect. It is noteworthy also that the improper storage (exposure to moisture) causes the production of dicumarol.<sup>18</sup>

Three other potential interactions were common: *Camellia sinensis* (black tea/green) with enalapril, *Pimpinella anisum* (anise) with estradiol and *Mentha x piperita* (mint) with omeprazole.

The excessive intake of *Camellia sinensis* (tea black/green) can be an increase in blood pressure, but this increase seems to be small and not necessarily maintained during long-term use. The presence of caffeine between the components of the black/green tea, which is an antagonist of endogenous adenosine is responsible for vasoconstriction increases blood pressure.<sup>17</sup> Hypertensive crisis may occur in these three women exposed to above interaction (Table 2), but as they reported that they never stopped using plants due to expression of any side effects, possibly, if there was an increase in blood pressure, was probably attributed to the drug in use, which was not being effective, or, if not often monitored the pressure, the interaction may have gone unnoticed. In this case, the doctor's ignorance about the interaction could induce him to increase the dosage of antihypertensive used, or add another medicine to treat user, making the most complex treatment and can cause adherence problems, besides representing higher economic impact to the system.



The active constituents of *Pimpinella anisum* (anise) seem shows estrogenic activity and can compete for the same estrogen receptor those hormonal drugs, and there may be synergism or antagonism, but the clinical relevance of this data is not fully elucidated, since this interaction is based only experimental evidence.<sup>17</sup>

Sharp increase in gastric pH caused by antacids may result in premature dissolution of the enteric coating and release of the oil of *Mentha x piperita* (peppermint) in the stomach, which increases the risk of heartburn with this formulation.<sup>17</sup> However, this women study used the tea plant, in this case, the small percentage or absence of oil after preparation is not enough to cause an interaction.

In addition, of the 59 women who use drugs, nine (15,25%) used at least one herbal medicine and concurrently, totaling six (66,7%) women exposed to interactions between herbal medicines and medicines with more than five (55,5%) are exposed to more than one interaction. 16 potential interactions averaging 3,17 interactions per woman were identified. For severity, it was found that one (6,25%) interaction has doubt about the result of the simultaneous, <sup>17</sup> 13 (81,25%) were moderate/significant risk and two (12,5%) interactions not severity.<sup>18</sup> Reports were found of the nine herbal analyzed, two had potential interactions with medications (Table 3).

Table 3 - Potential interactions between herbal medicines and identified in menopausal women registered in FHSs VII and VIII. Ijuí/RS, 2013-2014.

Phytotherapeutic	Medication	Effect	Severity	N (%)
	Omeprazol <sup>14,17</sup>	↓ effect of omeprazol aggravated	Moderate/significant	3 (15,9%)
	Enalapril <sup>18</sup>	bradycardia and hypotension	Not found	2 (10,4%)
	Fluoxetin <sup>14,16,18</sup>	↑ serotonin syndrome risk (hypertension, hyperthermia, myoclonus, mental status changes), ↑ risk of convulsions	Moderate/significant	1 (5,26%)
<i>Ginkgo biloba</i> (ginkgo)	Duloxetin <sup>16</sup>	↑ risk of convulsions	Moderate/significant	1 (5,26%)
	Paroxetina <sup>14,16,18</sup>	↑ risk of serotonin syndrome, ↑ risk of convulsions	Moderate/significant	1 (5,26%)
	Nortriptilina <sup>16,18</sup>	↑ risk of convulsions,	Moderate/significant	1 (5,26%)

		cardiac arrhythmias and side effects (dry mouth, tachycardia, urine retention, sedation) ↑ risk of convulsions, cardiac arrhythmias and side effects (dry mouth, tachycardia, urine retention, sedation) ↑ risk of convulsions	Moderate/significant	1 (5,26%)
	Amitriptilina <sup>16,18</sup>	cardiac arrhythmias and side effects (dry mouth, tachycardia, urine retention, sedation) ↑ risk of convulsions	Moderate/significant	1 (5,26%)
	Cytopram <sup>14,16</sup>	↑ risk of serotonin syndrome, ↑ risk of convulsions	Moderate/significant	1 (5,26%)
	Ácido acetilsalicílico (AAS) <sup>14-15-16-17-18</sup>	↑ risk of bleeding	Moderate/significant	1 (5,26%)
<i>Ginkgo biloba</i> (ginkgo)	Pregabalina <sup>16</sup>	↑ risk of convulsions	Moderate/significant	1 (5,26%)
	Clortalidona <sup>16</sup>	↑ blood pressure	Moderate/significant	1 (5,26%)
	Ciclobenzaprina <sup>16</sup>	↑ risk of convulsions	Moderate/significant	1 (5,26%)
	Diazepam <sup>14,16</sup>	↑ risk of convulsions	Moderate/significant	1 (5,26%)
	Atenolol <sup>18</sup>	↓ efficacy of diazepam aggravated bradycardia and hypotension	Not found	1 (5,26%)
	Hydrochlorothiazide <sup>14,16</sup>	↑ blood pressure	Moderate/significant	1 (5,26%)
<i>Uncaria tomentosa</i> (catclaw acacia)	Atenolol + chlorthalidone <sup>17</sup>	the additive effect ↓ of blood pressure	There is doubt about the simultaneous	1 (5,26%)

		use		
Total	16	-	-	19 (100%)

In a study conducted in Belo Horizonte/MG,<sup>35</sup> 45% of herbal users elderly were exposed to at least one drug interaction between herbal medicines and traditional medicines. In the present study was found an increased number of interactions exposure, most of which involved *Ginkgo biloba* and steady medication such as antidepressants and antihypertensive drugs, probably because these drugs were the most used after analgesics, women this study.

It was observed potential interaction between aspirin and *Ginkgo biloba*, since both interfere with blood clotting, therefore, when used concomitantly can cause synergism, increasing the platelet aggregation inhibition, and there is risk of bleeding. This is because the ginkgo extract contains ginkgolideum B, which is a potent inhibitor of platelet activating factor.<sup>14-15-16-17-18</sup>

Concomitant use of *Ginkgo biloba* and omeprazole may result in reduced efficacy of omeprazole, it may occur increased metabolism (hydroxylation) of omeprazole by inducing isoenzymes CYP2C 19 cytochrome P450.<sup>17</sup> The three women exposed to this interaction may have increased production of stomach acid and may have gastritis, reflux, among other symptoms.

When *Ginkgo biloba* is used with selective serotonin reuptake (fluoxetine, paroxetine, and citalopram) may increase the risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, altered mental status),<sup>14</sup> as well as seizures.<sup>16</sup> Symptoms usually occur within the first six hours after administration of the drugs, and the initial symptoms are tremor, akathisia and diarrhea.<sup>18</sup> These interactions, despite having moderate/significant severity, reinforce the importance of informing the doctor about the herbal drug administered concomitantly, since the serotonin syndrome can be fatal.

Some preparations of *Ginkgo biloba* can cause seizures, and use it with duloxetine, pregabalin, cyclobenzaprine, diazepam, amitriptyline and nortriptyline can increase this risk. Among the constituents of Ginkgo, there are varying amounts of 4-O-methyl pyridoxine (ginkgotoxin), a neurotoxin mainly found in the seeds and in minor amounts in the leaves. In vivo, 4-O-methyl pyridoxine competes with vitamin B6, which causes indirect inhibition of glutamate decarboxylase, which in turn results in the induction of seizures by decreasing levels of gamma-aminobutyric acid (GABA) in the brain. The interaction may be more likely in the elderly, individuals with a history of seizures, or disease that affects the central nervous system, such as a brain tumor or cranial trauma.<sup>16</sup> In addition, concomitant use with amitriptyline and nortriptyline can trigger cardiac arrhythmias and side effects with xerostomia, tachycardia, sedation and retention of urine and 18 when used concurrently with diazepam may occur decreased effect of this drug.<sup>14</sup>

On the interactions of *Ginkgo biloba* with antihypertensive drugs, it was found that

when administered concomitantly chlorthalidone or hydrochlorothiazide may occur change in the effects of these drugs, which may cause increased blood pressure.<sup>14,16</sup> With atenolol and enalapril may experience worsening of bradycardia and hypotension, but the mechanism of these three interactions is unknown.<sup>18</sup>

As the herbal *Uncaria tomentosa* (cat's claw), it was found that can interact with chlorthalidone, since it has hypotensive effect, which occurs due to the vasodilation effect and the momentary reduction in the frequency and force of cardiac contraction. Therefore, there may be additive effects in lowering blood pressure with concomitant use of these two substances.<sup>17</sup> The occurrence of this interaction is characterized by hypotension, weakness, dizziness, and other symptoms, which may be related by the user or the healthcare team with excess drug effect in use.

In this study the interactions were identified in which women studied are exposed; it is difficult to detect the actual occurrence of an interaction, especially for biological variation observed among patients. Moreover, it is expensive and requires complex and specific analytical methods for estimating which the active principles present in plants and the concentration of each when used as teas, because the method of extraction affects the composition and therefore its potential interaction. Still, the plant extracts differ from drugs, because they are complex mixtures of various bioactive compounds, making it difficult to evaluate the contribution of each constituent in the overall activity.<sup>17</sup>

In this context, the indiscriminate use of plant and/or herbal medicines to treat diseases should be viewed more closely by the population, but apparently harmless plants, and used as a medicament may be demonstrably hazardous, depending on the way they are administered, and this risk is more present when the user combines use with drug.<sup>2</sup> In this study, few women used herbal medicines, but a high percentage used plants, averaging four/person and about 70% of women used drugs, averaging three/person, exposing the interactions with different degrees of severity. It is noteworthy that identified in interviewees' reports which, according to them, the use of plants and/or herbal concomitant drug does not imply risks to health and the plant complements or enhances the action of the drug. The results of the interactions which women are exposed, shown in Tables 2 and 3 indicate the need for interventions related to pharmacotherapy, in order to avoid possible damage to health and optimize the effect of both the drug as plant and/or herbal. For such action is necessary to science both to prescribers about the products in use, for the women who practice self-medication with herbal plants and seeking rationalization of therapy.

Undeniably, medicinal plants and herbal medicines play an important role in therapy, however, the belief "that is natural does not hurt" causes the majority of the population does not relate to the possibility of adverse events and this may be one of the reasons to consider irrelevant communicate the doctor on the concomitant use of medicinal products, as observed in this study. Still, free access to the plants, such as in supermarkets, fairs, cultivation in their own homes, makes the population believe that



guidance on the use are unnecessary.

In addition, the population in some cases, do not have knowledge of the species and quality of the plants you are using, which could be achieved with the adoption of Living Pharmacies, because through them, medicinal plant gardens could be installed next to health units and community centers providing medicinal plants for free to the population, which could make your home pharmacy with plants certified by botanists and even women could be educated on best practices of use, with the design and proper dosage, guided by a responsible pharmacist.<sup>24</sup>

From the results obtained and considering that this study was conducted in FHSs, it is necessary to propose intervention strategies to avoid possible drug interactions and self-medication with medicinal plants and herbal medicines. In this sense, it is suggested actions aimed at raising awareness and training of physicians regarding the safe use of medicinal plants and herbal associated or not the drugs, which could be launched from the herbal medicines listed in RENAME. It would also be important to train community health workers using as a working tool the materials of the Ministry of Health, as PNPIC and official lists of medicinal plants, in order to subsidize them to guide and answer questions from users about it, and to identify user demands and present them to health teams. Other important aspects include discussing the possibility and interest in implementing a Living Pharmacy in the city, alert users to inform the doctor about the concomitant use of medicinal plants, herbal and medicine, exercise caution with elderly patients and polymedicated and even inform the population about risks related to the use of "natural products".

The limitations of the study, it is emphasized that the sample was small, was not analyzed the dosage of herbal medicines and drugs, or the method of preparation of tea, or the time of use thereof by the interviewees, which are factors that do not directly influence identification of potential interactions, but in consideration thereof, which can be performed in future studies.

## CONCLUSION

The popularity of using "natural products" is important to the understanding of the potential interactions between herbal medicines, herbal medicines and medicines, as well as monitoring the concurrent use by health professionals, to identify the occurrence of interactions that can compromise the user's health.

This research revealed that women studied are exposed to interactions resulting from the use of medicinal plants and herbal concomitant drug, indicating high frequency of this adverse event. Most of the identified interactions are moderate/significant risk, which can cause damage to the user, followed by the lower risk of interactions, which should also be analyzed with caution, since in many cases may imply additional treatment, ie when reduction occurs the effect of some of the medications used the trend is that another drug is added to the treatment or the drug may have questioned its effect may be replaced.

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Contact of the corresponding author:  
Gabriela Tassotti Gelatti  
Rua Procópio Gomes, 221. Bairro São Miguel. CEP: 98025-055. Cruz  
Alta/RS Brasil. E-mail: gabriela.gelatti@hotmail.com  
Telefone: (55)3324-2091