ORIGINAL ARTICLE

Drug interactions between plant-based natural products and medicines used by elderly in the city of Diadema, Brazil

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ABSTRACT

Elderly people often combine the use of synthetic drugs with plant-based natural products (PBNP) to treat diseases, especially chronic ones. However, the association of both can cause adverse drug events, which are generally undesirable and harmful to health, and ethnopharmacovigilance studies aimed at this group are important. In view of the above, the objective was to investigate possible drug interactions (DI) between PBNPs and synthetic drugs, according to reports by elderly people, supported by data from the scientific literature. To this end, meetings were held at the Centro de Convivência Municipal da Melhor Idade in Diadema-SP, involving 30 elderly people, using focus groups, semi-structured interviews and field diaries. Seven reports of possible DIs were obtained by the interviewees, involving seven PBNPs, of which four (chamomile, boldo-de-Chile, clove, hibiscus) were supported by the scientific literature, indicating possible DI with antihypertensive, antidiabetic and anticholesterolemic drugs. For three of the DIs, the events were unwanted, while for one of them it was considered positive by the user, in the case of hibiscus as an adjunct in the treatment of arterial hypertension. It is concluded that the data presented should support the investigation of other reports from elderly people, expanding our limited knowledge about DIs between PBNPs and synthetic drugs, in general, considered safe by the population.

Keywords: elderly, medicinal plants, ethnopharmacovigilance, drug interactions.

INTRODUCTION

Phytotherapy is a branch of allopathic therapy that uses medicinal plants, in their various forms, here called Plant-based natural products (PBNPs), for the treatment and prophylaxis of diseases, or even for a better quality of life. PBNPs can be divided into: 1- medicinal plants in natura or in a stabilized and preserved form, called plant drug; 2- manipulated herbal medicines, under prescription by a legally qualified professional; 3- industrialized herbal medicines, divided into traditional herbal products and herbal medicines, notified or registered in Brazilian Health Regulatory Agency (Anvisa) (ANVISA 2014; Oliveira et al. 2016); and 4- other different types of products of plant origin that are also marketed for therapeutic purposes, and to improve quality of life and health, many of which are irregular or outside health regulations (Passos et al. 2018).

It is important to highlight that the countries that historically present greater evidence of the use of medicinal plants are those in development, because the lower-income population has limited access to industrialized medicines (WHO 1993; Chen et al. 2016). In the case of herbal medicines, in general, they end up being more expensive than synthetic medicines, making them less accessible to these populations, who end up looking for economically viable alternatives. "Miracle" medicinal plants, "panaceas" and "novelties" ("fashionable plants") also arouse public interest. Finally, there is also the movement of society known as "green wave" which is significantly expanding interest in plant-derived therapeutics as a "natural" alternative to synthetic drugs, with their usual list of side effects (Handa and Kaul 1996; Desmarchelier 2010). This scenario ends up favoring and stimulating the increased use

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of PBNPs, of which most of the plant species and associations are devoid of quality, efficacy and safety studies, in addition to strengthening an unreliable and risky informal market (Thakkaret al. 2020).

Although PBNPs are increasingly routinely used by a significant portion of the population, most users do not have minimal knowledge about them and their risks, ignoring all parameters that involve safety, efficacy and quality, such as the possibility of acquiring a counterfeit, adulterated, contaminated, degraded, causing possible drug interactions, toxic effects, allergenic potential, among other risks (Soares et al. 2013). This lack of concern is due to the fact that for many people phytotherapy is seen as a "natural medicine", as something beneficial, without considering that PBNPs have bioactive chemicals, which can also be harmful to health (Oliveira & Lehn 2015). Among the elderly, this risk is even greater, due to their fragile bodies by age, and by the use of a greater number of medications (Silva and Araújo 2015).

The aging process is usually related to the emergence of diseases, where the elderly population appears with the highest rate of chronic non-communicable disease (NCD), and many elderly people may have two or more NCDs concomitantly (Roth et al. 2018). The use of multiple medications by older people results in greater physiological fragility (Muniz et al. 2017) and increased exposure to possible Adverse Drug Events (ADEs) due to drug interactions between different drugs (Pagno et al. 2018; Rocha et al. 2021).

The possibility of such events is amplified when these synthetic drugs are consumed simultaneously with PBNPs, making their uses even more susceptible to potentially dangerous ADEs (Carneiro and Comarella 2016).

The World Health Organization defines an adverse drug event (ADE) as: "any undesirable medical occurrence that may occur during treatment with a drug, without necessarily having a causal relationship with this treatment" (WHO 2002). The main factors that influence the occurrence of ADE are the patient's age (the elderly are more likely), multiple conditions (multimorbidity) and polymedication (above four medications significantly increases the occurrence) (Zazzara et al. 2021). Drug interactions (DIs) are one of several types of adverse events, as described Varallo and Mastroiani (2013), that can potentiate the effect of the concomitant use of these drugs, leading to intoxication (INT), or even inhibit the desired effect, which may be the cause of therapeutic ineffectiveness.

Generally, popular knowledge about the therapeutic possibilities and restrictions on the uses of medicinal plants comes from the elders in traditional communities, with elderly people in the urban environment (Carvalho et al. 2015). The cultural transmission of such knowledge allows a person to acquire information throughout life and in many ways. In addition to relatives, neighbors, friends, television and radio (Soldati 2016), they can obtain knowledge through information and dissemination networks, such as health pastorals (Siqueira et al. 2018) and the increasingly common dissemination, through the internet (Passos et al. 2018). So, elderly in general, are an important source of knowledge about the interactions resulting from the concomitant use of PBNPs and synthetic drugs, due to the time and condition of life that result in experiences in the daily use of these drugs.

The aim of this study was to investigate possible DIs from the concomitant use of PBNPs and synthetic drugs (conventional drugs), according to reports from elderly people in Diadema, SP, especially those polymedicated, that is, those who use daily 2 or more medicines for the treatment of chronic diseases.

MATERIALS AND METHODS

The present study was approved by the Research Ethics Committee of the Federal University of São Paulo – UNIFESP (CEP No. 0496.0052.05/2018; CAAE: 891123118.8.0000.5505), and all study participants signed the Free and Informed Consent Form.

Data collection was carried out among people aged 60 years or older, registered at the Centro de Convivência Municipal da Melhor Idade (CCMI) in Diadema, SP, Brazil, which has approximately 80 people. In May and June 2018, four informative posters were posted on the premises of the aforementioned Center (one every 15 days), inviting visitors to participate in a survey entitled: "Medicinal Plants".

Four events were held in a CCMI room for data collection, in the format of conversation circles with a maximum of 10 people in each one, so that participants could interact in depth and hear their case reports.

During these meetings, a technique called focus group was used, suggested by Leny (2009) and defined as a qualitative research technique, derived from group interviews, that collects information through group interactions (Morgan 1997). According to Kitzinger (2000), its main objective is to collect and gather information about a specific topic among a group of people at the same time, so that one can reach and understand their beliefs, perceptions and attitudes in relation to the topic addressed by a researcher. The author emphasizes the qualities of this type of methodological approach favoring the development of studies when respondents do

not read/write; and encouraging people who are reluctant to participate in interviews and/or those who think they have nothing to offer.

Thus, each meeting lasted from 90 to 110 min, divided into two stages. In the first 60 min, a standard script was followed: the researchers explained the difference between "medicinal plant", "vegetable drug" and "industrialized herbal medicine", showing an example of each kind of PBNP, through color photos arranged on a cardboard with: i) different parts of plants *in natura*, ii) sachets with dehydrated, scraped or pulverized plants (we are calling here "vegetable drugs") and iii) herbal medicine box, respectively. Then, the researchers asked the participants the following question: "Have you ever observed any change in the effect of the drug from the "pharmacy" when you used some "medicinal plant" or its derivatives together?".

This sentence was written on a blackboard and placed next to the table where the interviewees were gathered, so that it could serve as a stimulus for the reports during the meetings. Once stimulated, each participant counted the cases in which they observed a positive or negative relationship of the concomitant use of PBNPs and synthetic drugs, which had occurred with themselves and/or with a family member, neighbor, among others. All these reports were considered in the present analysis. During these reports, the researchers asked several questions, noting the responses of the elderly people, as well as their own perceptions in a field diary; expanding the possibility of future qualitative analysis (Malinowsky 1990). In addition, the personal data of all participants were also collected, through a Personal Data Sheet (name, sex, age, place of birth, education, occupation and from whom they learned about the use of plants).

In the final 50 min of the meeting, semi-structured interviews were carried out (Bernard 1988) only with those people who reported any DI between PBNP and synthetic drugs, in order to better detail the information given in the first part of the meeting. These interviews followed a script of open questions using a Data Sheet on Drug Interactions, containing the following questions (name of the synthetic drugs and PBNPs used, for what purpose the drugs were used, type of interactions observed, time of use, part of the plant used, quantity, route of administration, method of preparation, dose, duration of the undesired effect, who it happened to, whether it was necessary to go to the emergency room, and origin of the plants/drugs). These data, in addition to being recorded in the aforementioned interview form, were also described in a field diary, including the participants' body expressions (Malinowsky 1990).

At the end of the meeting, the researchers provided a classic book on medicinal plants by Lorenzi and Matos (2008), with photos of the plants mentioned to assist in the indirect identification of plants, as indicated by the interviewees.

The data obtained from notes in field diaries and interviews offered a rich source for qualitative analyses. The mentioned notes were submitted to content analysis, being condensed and coded, in order to facilitate the finding of thematic categories in the data obtained, allowing a reflection on the results, allowing inferences and interpretations (Huberman and Miles 1994).

From the identification of plants through the photos of the book by Lorenzi and Matos (2008), bibliographic surveys were carried out in October 2021, in order to verify the existence of scientific studies on IMs involving PBNPs and the respective synthetic drugs reported by the interviewees.

To this end, two sites were consulted that provide data on adverse reactions, drug interactions, contraindications and other adverse events involving plants and synthetic drugs, they are: 1. Drugs.com - (www.drugs.com) and 2. Micromedex - (http://www-micromedexsolutions-com.ez69.periodicos.capes.gov.br/micromedex2/librarian).

Also, in order to verify the existence of scientific studies on DIs involving PBNPs and the respective synthetic drugs reported by the interviewees, a Boolean search was carried out in the "Scopus" database, considering the terms: "Genus of the plant" AND "specific epithet" AND "Substance name" present in the reported synthetic drugs. Thus, for example, for the species related to the hibiscus plant, whose scientific name is *Hibiscus sabdariffa*, the following search was used: hibiscus AND sabdariffa AND enalapril.

In order to expand the possibilities of finding data that met the expectations of the present study, further searches were performed in the same database containing the following terms: "interactions", "adverse reactions" and "contraindications", as shown below.

1. "plant genus" AND "specific epithet" AND interactions;
2. "plant genus" AND "specific epithet" AND adverse AND reactions;
3. "Plant genus" AND "specific epithet" AND contraindications.

The inclusion criteria for these searches were: scientific articles, including reviews, without limiting time, in Portuguese, English and Spanish. And the exclusion criteria were: i) books and book chapters; ii) articles that, despite having some discussion about the possible drug interaction, did not present results that made it possible to establish the cause-effect relationship desired here; and iii) other languages. Through a descriptive review of the interactions of each mentioned species, we

sought to extract and analyze the largest number of articles, performing a qualitative content analysis (Mayring 2014).

A difficulty in this study was related to the lack of collection of plant material, which was not possible due to the difficulty of the interviewees in obtaining the specimens, especially because they used plants from stores. In this way, we limit ourselves to accepting the indication of the plant reported only by the popular name and by the botanical identification carried out through figures by the participants themselves, and in the criterion of taxonomic clues from the data provided by them and obtained by consulting the specialized bibliography.

RESULTS AND DISCUSSION

Thirty elderly people participated in the research, being 2 (6.7%) male and 28 (93.3%) female. This data is a reflection of the composition of the CCMI, mostly female, which is a situation also found in Brazil among the elderly population, with a greater predominance of females over males (IBGE 2018). According to pharmacoepidemiological studies, women are also the ones who make the most use of medicines and health services, since they prevent themselves more and are less exposed to the risk of death compared to men (Muniz et al. 2017).

Approximately 80% (n=24) of respondents who reported making concomitant use of PBNPs and synthetic drugs did not complete elementary school. This characteristic can influence the understanding and correct follow-up of the prescription, allowing changes or errors in the use of medicines. The ingestion of larger doses of medication due to forgetfulness or negligence is one of the main factors of unintentional intoxication in elderly people (Silva et al. 2012). Only one elderly person reported using herbal medicine, but most participants were unaware of this denomination.

The average age of the participants was 73.4 years, with 71.1 years being the average of those who used some PBNPs concomitantly with synthetic drugs. It was found that 26 (86.7%) of them used at least one synthetic drug prescribed to control diseases, with hypertension being the most common. Similar data were obtained in other studies, such as the one by Coelho Filho et al. (2004) in the northeast region of Brazil, where 80.3% of the elderly used at least one prescribed medication.

Elderly people with advanced ages (>70 years old) use a greater number of medications, which can trigger several serious consequences, such as an increase in adverse reactions (Silva et al. 2012). Added to this, the substances present in PBNPs can also potentiate these effects, which should be taken into account, considering that studies point to the greater use of medicinal plants as therapy by the elderly public (Santos et al. 2017).

Among the participants, 19 (63.3%) reported using plants and/or vegetable drugs during the four meetings held in this study, while Machado et al. (2014) identified a higher number for the elderly (76.7%; n= 224). Among those who reported the occurrence of DIs between PBNPs and synthetic/herbal/phytopharmaceuticals (active ingredients isolated from plants), there were only 7, representing almost ¼ of the participants. This number can still be considered high, since most users of medicinal plants hardly observe and associate risks with the use of natural products. In this sense, a new concept - Ethnopharmacovigilance - was recently suggested by us, exploring the need to approach and record the adverse events observed during the use of different natural resources in traditional medicine and academia. So, Ethnopharmacovigilance is a branch of the ethnosciences that is concerned with the collection, collation, interpretation and analysis of traditional knowledge relating to traditional medicines derived from plants, animals and other natural resources to enhance understanding of the safety and harms profile of traditional medicines, including in relation to their use by traditional knowledge holders and other indigenous groups (Rodrigues and Barnes, 2022).

Data on the popular name, probable scientific name of these plants, reason for use, origin of the plant, report of possible interaction, form of preparation, part used, duration of use, dose, in addition to the personal data of the participants who made these reports, they can be observed in Table 1, namely: boldo-do-chile - *Peumus boldus* Molina; chamomile – *Matricaria chamomilla* L.; clove – *Syzygium aromaticum* (L.) Merr. & L.M.Perry; hibiscus – *Hibiscus sabdariffa* L.; jucá – *Libidibia ferrea* (Mart. ex Tul.) L.P.Queiroz; hand-of-God – *Tithonia diversifolia* (Hemsl.) A.Gray; and yacon – *Smallanthus sonchifolius* (Poepp.) H.Rob. The full report on such interactions is presented in Table 1 (Supplementary Material).

Table 2 presents the data found in the scientific literature on contraindications, adverse reactions and drug interactions on 4 plants - boldo, chamomile, hibiscus and clove, while for the other plants - yacon, hand-de-Deus and jucá, no such information was found. That is, three of the seven interactions reported between PBNPs and synthetic drugs did not present any type of formal record on the consulted websites or in studies published in the Scopus database on the subject. However, such information should not be neglected, considering that in two of these cases users had to go to the emergency room. It is recommended to inform the

Table 1. Information on the combined use of plant-based natural products (PBNP) with synthetic drugs and other substances or products by users of Centro de Convivência Municipal da Melhor Idade (CCMI) in Diadema, SP/Brazil.

Combined use of PBNP with synthetic/herbal/substance drugs	Possible scientific name of the plant species (PBNP type)	Personal data	Reason for use	Origin of the plant	Report	Way of preparation	Used part	Duration of use	Dose
Boldo do Chile + Captopril + Simvastatin + Acetylsalicylic acid + "Grandma's Syrup"*	*Peumus boldus* Molina (medicinal plant)	Female, 74 years old, full HS, pensioner	Cough	Purchased	vomited after ingesting	Tea	Sheet	1 only time	6 sheets
Chamomile + Hydrochlothiazide + Losartan	*Matricaria chamomilla* L. (vegetable drug)	Female, 74 years old, incomplete ES, Retired	high pressure control	Purchased	Shortness of breath, increased heart rate and chest pain	Tea	Flower	Frequent	1 tea bag sachet
Clove + Hydrochlorothiazide + Losartan + Simvastatin + Atenolol + Amlodipine + Metformin + Hesperidin**	*Syzygium aromaticum* (L.) Merr. & L.M.Perry (medicinal plant)	Female, 68 years old, incomplete ES, Retired	high pressure control	Purchased	Hypertension; trip to the emergency room	30g of cloves per 1L of water	flower bud	1 month	30 grams
Hibiscus + Enalapril	*Hibiscus sabdariffa* L. (medicinal plant)	Female, 66 years old, Full HS, Housewife	high pressure control	Bought at home herbs	The medicine was no longer having an effect, he started to drink the tea and the pressure normalized	infusion/ tea	Flower	1 week	3 flowers per glass of water
Jucá + Losartana	*Libidibia ferrea* (Mart. ex Tul.) L.P.Queiroz (medicinal plant)	Female, 83 years old, incomplete ES, Housewife	diabetes control	Brought from Parintins-AM by the daughter	Severely leaked bowel	Soaked in water for 1 day and ingested it	Seed	3 months of continuous use	1 liter of water for 4 pieces of the seed
Hand of God + Metformin	*Tithonia diversifolia* (Hemsl.) A.Gray (medicinal plant)	Female, 61 years old, incomplete ES, Day laborer (with brother)	diabetes control	collected at home	Excessive weight loss and sudden drop in blood glucose, he was hospitalized for a week	Macerated and mixed with water at room temperature	Sheet	1 time a day, periodic use	200 ml of water + 2 leaves of the plant

Table 1. continued

Yakon + controlled insulin	*Smallanthus sonchifolius* (Poepp.) H.Rob. (Medicinal plant)	Male, 72 years old, incomplete ES, Retired	diabetes control	Purchased	Hypoglycemia and had to go to the emergency room	Crude	Source	did not know how to report	did not know how to report

Caption: *Irregular Herbal Product; **Phytopharmaceutical (active ingredient obtained from plant species); HS - high school; ES - elementary school.

doctor and pharmacist about the use of these plants together with synthetic drugs, in addition to the effect caused by this combination. The citizen himself, or health professionals when informed, must report these adverse events in ANVISA's VigiMed System (2018).

Generally, the patient does not communicate to the doctor or pharmacist the concomitant use of medicinal plants associated with the prescribed synthetic drugs, especially in the case of irregular natural products (outside of health legislation), which makes it difficult for health professionals to adequately guide their use. correctness of medicines, as well as the recording of adverse events, which would contribute to the pharmacovigilance of medicinal plants and herbal medicines (Leal and Tellis 2015).

Therefore, it is highly recommended that physicians be advised about the concomitant use of PBNPs and synthetic drugs, especially if there is any type of harmful adverse event, as was the case with most of the reports described above. It is also important to emphasize the negligence towards PBNPs and the consequences of this, since DIs and later intoxications or damage to health can occur. The assumption that PBNPs do not have side effects because they are "natural products" needs to be demystified and adequately disseminated to the population, so that there is an awareness of the problem (Debbie et al. 2012).

Likewise, it is extremely important that the prescriber asks the patient about the use of other plant-based natural herbal products, as doctors usually only ask if the patient uses other medicines, which makes patients not feel provoked to inform about the use of plants and other products, which in the understanding of many would not be within the scope of medicines (Haraguchi et al. 2020).

A discussion about each plant mentioned and their interactions, in the context of case reports, is presented below.

Chilean Boldo (*Peumus boldus* Molina / Monimiaceae)

The interviewee's report was about vomiting in case of concomitant use of boldo leaves in tea with simvastatin, captopril, aspirin and "Grandma's Syrup".

According to the website "drugs.com" this plant can cause liver toxicity, therefore, the possibility of this reaction having been caused by this plant cannot be ruled out, regardless of the concomitant use with the aforementioned synthetic drugs, in addition to being associated with the use of a product identified as irregular, called "Grandma Syrup". Also, the simvastatin package insert indicates "vomiting" as a rare adverse reaction. Therefore, it is possible that the episode "vomiting", presented by the interviewee, was due to the plant or the simvastatin alone, to the irregular product without any safety, efficacy and quality standard, or even the combination of the entire therapeutic repertoire used simultaneously. simultaneously.

Irregular products such as "Grandma's Syrup" are known for the mixture of many medicinal plants, in the cultural and popular logic of bottles, in which the more plants the better the effect, which offers a huge health risk due to the lack of identity and quality of plant materials used, associated with the risk of multiple and unknown interactions between the components and the expansion of possible side effects (Passos et al. 2018). It is also important to note that the interviewee did not associate the adverse reaction with any of the synthetics she used.

Regarding the risks of interactions, it is important to highlight that it has already been reported that the use of boldo-do-chile with warfarin promotes an increase in the international normalized ratio (INR), possibly due to the additive pharmacological effect of boldine and secoboldine, which have the ability to inhibit platelet aggregation, increasing the anticoagulant potential (Basila et al. 2005). In the package insert for simvastatin, it is recommended to inform the doctor when using anticoagulant medications such as warfarin; whileone of the contraindications found in the package insert for aspirin is that it should not be used in patients who are using anticoagulants, as it may increase the risk of bleeding in certain cases. Therefore, the concomitant use of simvastatin, aspirin and boldo does not seem to be favorable, especially due to the

risk of decreasing platelet aggregation.

Clove (*Syzygium aromaticum* (L.) Merr. & L.M.Perry / Myrtaceae)

According to the report, when using clove inflorescences to control high blood pressure, it ended up potentiating the symptoms of hypertension, having to go to the emergency room.

Although no information consistent with the increase in blood pressure is present on the websites consulted, in the *in vitro* study by Foster et al. (2003), this plant showed a high degree of inhibition of all cytochrome P450 (CYP) isoforms tested (2C9, 2C19, 2D6 and 3A4), suggesting that it can interfere with the metabolism of several drugs, mediated by CYP. It is noted that the interviewee in this case uses several medications: hydrochlorothiazide, losartan, simvastatin, atenolol, amlodipine, metformin and

Table 2. Information on contraindications, adverse reactions, drug interactions found in the scientific literature for the indicated plants by users of Centro de Convivência Municipal da Melhor Idade (CCMI) in Diadema, SP/Brazil.

	Peumus boldus Molina (Chile's Boldo)	*Syzygium aromaticum* (L.) Merr. & L.M.Perry (clove)	*Hibiscus sabdariffa* L. (Hibiscus)	*Matricaria chamomilla* L. (Chamomile)	*Tithonia diversifolia* (Hemsl.) A. Gray (God's hand); *Smallanthus sonchifolius* (Poepp.) H.Rob. (Yakon); *Libidibia ferrea* (Mart. ex Tul.) L.P.Queiroz (Jucá)
Contraindications	Liver and bile duct diseases, including gallstones[1]	Undocumented[1]	Unidentified[1]	People with hypersensitivity to pollens[1]	No information[1]
	Severe liver disease, bile duct obstruction, kidney disease[2]	Hypersensitivity to clove or its eugenol-type essential oil[2]	No information[2]	Hypersensitivity to chamomile or other members of the Asteraceae family[2]	No information[1]
Adverse reactions	Whole-body allergic reaction, heart rate disorders, and liver toxicity[1]	Contact dermatitis[1]	No records[1]	Use of tea and essential oil resulted in anaphylaxis, contact dermatitis and other severe hypersensitivity reactions[1]	No information[1]
	kidney irritation[2]	The essential oil can be irritating to mucosal tissues, inhalation of volatile compounds from clove cigarettes can cause hemorrhagic pulmonary edema or other respiratory problems, mild hypertension, mild euphoria, respiratory distress and dermatitis[2]	No information[2]	Anaphylaxis, high-dose vomiting, conjunctivitis, contact dermatitis/eczema, rhinitis[2]	No information[2]

Table 2. continued

	Ingestion may increase the anticoagulant effect of warfarin[1]	Not well documented[1]	Hibiscus drinks may reduce chloroquine plasma levels, decreasing its effectiveness[1]	Possible reactions have been reported with Warfarin or Cyclosporine, avoid concomitant use[1]	No information[1]
Drug interactions	Anticoagulants, low molecular weight heparins, antiplatelet agents and thrombolytic agents[2]	Anticoagulants, low molecular weight heparins, antiplatelet agents and thrombolytic agents[2]	No information[2]	Asthma, interaction with anticoagulants[2]	No information[2]

Subtitle:1. Drugs.com - (www.drugs.com); 2. Micromedex - (http://www-micromedexsolutions-com.ez69.periodicos.capes.gov.br/micromedex2/librarian).

hesperidin, some of which are metabolized in the liver, showing a relationship with this cytochrome. In the same work, the author says that the clove, if used in combination with one or more conventional therapeutic products or other natural products, may have even greater potential. That is, the higher the rate of drugs used and their duration, the greater the chance of interactions between the products.

For this same plant, a report was found of a man who had a toothache and chewed the clove to relieve the pain, and after 3 days he had oral lesions, presenting an erythema multiforme. The condition worsened when he received gentamicin from a doctor. The likely etiologic agent of the wounds is believed to be cloves, intensified by the interaction with gentamicin (Gantala et al. 2015). The essential oil of this plant, as well as its active ingredient eugenol, are pungent and known for the risk of causing irritation of the mucous membranes and contact dermatitis, especially in high doses and for hypersensitive patients (Ulanowska and Hello 2021).

Hibiscus (*Hibiscus sabdariffa* L. / Malvaceae)

Hibiscus was the only example in this study whose MI with synthetic drugs could be considered beneficial, in this case for controlling hypertension, contributing to the regulation of blood pressure in conjunction with enalapril.

Although the information contained in the websites consulted is almost non-existent, several scientific studies were found relating the action of hibiscus to the control of hypertension. In one of them, Ondieki et al. (2017) indicate antihypertensive activity of the plant similar to captopril, and that concomitant use with Hydrochlorothiazide increases urine output. Another study developed by Ndu et al. (2011) established a significant change in both the pharmacodynamics and the pharmacokinetic indices of hydrochlorothiazide, caused by the plant extract when administered concomitantly. Another double-blind clinical trial for hypertension showed positive results, and no adverse clinical or metabolic effects were observed in them (Herrera-Arellano et al. 2007).

The report presented in the present study as well as the other studies presented above point to benefits in the concomitant use of hibiscus with some synthetic drugs. In these cases, the possibility that beneficial IMs can be explored in order to decrease the dose, and consequently the toxicity of synthetic drugs, is discussed here.

However, the following studies point to possible negative IMs involving this plant. Ondieki et al. (2017) and Showande et al. (2017) reported the inhibitory potential of hibiscus in relation to several isoforms of cytochrome P450, which is the main enzyme of drug metabolism used in the treatment of chronic diseases, interfering with the metabolism of drugs for diabetes and hypertension, being a possible cause of events adverse to these drugs. Showande et al. (2017) concluded from preclinical and clinical studies that hibiscus water drink caused a significant plant-drug interaction, resulting in reduced exposure to simvastatin in humans. Jacquin-Porretaz et al. (2017) reported that a lung cancer patient treated with erlotinib using concomitant daily self-medication of hibiscus petal tea had a sudden severe adverse skin effect. When she stopped drinking the tea and treated herself with ciclopirox olamine and clobetasol propionate, her condition was reversed. Nowack and Nowak (2005) reported three case studies of patients who received kidney transplants, where beverages containing plants such as hibiscus and chamomile influenced

cyclosporine metabolism, immunosuppressive drug during the treatment of these patients.

Cancellara et al. (2019) highlight Hibiscus as the second most studied plant after green tea for weight loss, and its importance against inflammation, obesity, dyslipidemia, hypertension and liver diseases, can be consumed with some care in relation to high doses and in the gestational period, without highlighting possible interactions, but, emphasizing the need for clinical trials focused on its safety and efficacy, lacking only to highlight the importance of pharmacovigilance.

According to Carvalho et al. (2021), the constituents considered responsible for the pharmacological actions of Hibiscus are anthocyanins, predominantly cyanidin-3-sambubioside and delphinidin-3-sambubioside. In this review article, the authors also highlight the vascular action in hypertensive rats, demonstrating a vasodilating effect on the isolated aortic rings of rats, as a function of the endothelium-derived relaxing nitric oxide-cGMP (cyclic guanosine monophosphate) pathway and calcium inhibition (Ca^{2+}); and that in experimental studies it was found that hibiscus tea proved a reduction in blood pressure showing an efficacy similar to captopril, but less effective than lysopril.

Chamomile - *Matricaria chamomilla* L.

The report related to chamomile was unusual, as the plant tends to have a calming effect, being able to lower blood pressure through a hypotensive action, however, the interviewee reported a hypertensive effect of the plant.

In the *in vivo* study of Budzinski et al. (2000), chamomile showed relatively high cytochrome P450 3A4 (CYP3A4) inhibitory capacity. This finding may be linked to the fact that some of the antihypertensive drugs are metabolized in the liver and are directly related to the CYP (Péres et al. 2003). In other words, the ingestion of chamomile tea may have inhibited the action of the medication that controls hypertension, causing its activity to be reduced, generating the elderly woman's discomfort, causing the symptoms reported by her: chest pain, lack of air and increased heart rate. In addition, potential CYP450 interactions of chamomile extracts have been described in post-kidney transplant patients who are treated with high doses for long periods (EMA-HMPC 2015).

In another case report in the literature, a 70-year-old woman had a mitral valve implanted and arrived at the emergency room with a cough, expectoration of yellow sputum and difficulty sleeping. The team diagnosed an upper respiratory tract infection; and she was discharged without antibiotics. A few days later, she returned with a bruise.retroperitoneal in the pelvis and bleeding, with an increase in INR. The occurrence of this hemorrhage was attributed to the simultaneous and excessive use of chamomile products (skin lotion and tea including camphor) and Warfarin. It was believed that the coumarin constituent of chamomile, a minor component of the plant, may have acted in synergy with warfarin., resulting in anticoagulant action, supratherapeutic, which would explain the increase in its blood clotting index (Segal and Pilote 2006).

For the other plants

The three plants, God's hand (*T. diversifolia*), Yacon potato (*S. sonchifolius*) and jucá (*L. ferrea*) were reported in the present study as supporting the treatment of diabetes. In fact, the first two have preclinical studies demonstrating their hypoglycemic activity. So, the plant God's hand (*T. diversifolia*) popularly used in Brazil and around the world for diabetes control (Ajao and Moteetee 2017), had its report related to severe hypoglycemia, with hospitalization/hospitalization, possibly due to the potentiation of the effect of metformin, which was being consumed concomitantly by the elderly woman. Its hypoglycemic activity has been demonstrated in preclinical studies (Fauziyah et al. 2018; Ejelonu et al. 2022), so in this case an alert should be linked to the risk of self-medication for people with chronic endocrine diseases, as well as the need to monitor the clinical and biochemical parameters of these patients. The potato yacon (*S. sonchifolius*) has several studies proving its hypoglycemic activity, as presented in the review conducted by Contreras-Puentes and Alviz-Amador (2020). While the jucá plant (*L. ferrea*), which was also used for diabetes, resulted in diarrhea. Although traditionally it is reputed to be anti-diarrheal (Ferreira and Soares 2015), the fact that diarrhea occurred due to the interaction between the plant and losartan, also used by the elderly in question, cannot be ruled out.

Return of Work to the Community

The present work was the result of an extension activity, being demanded by the elderly from the Centro de Convivência Municipal da Melhor Idade (CCMI) in Diadema, SP, Brazil. In 2017, the coordinator of that center approached UNIFESP, through the extension project called Plantas Consciência, so that the elderly could obtain guidance on the rational use of medicinal plants. From the meetings between the elderly and UNIFESP, the need arose to deepen the exchange between the knowledge of each party; since the elderly had valuable experiences about the interactions between synthetic drugs and medicinal plants and/or herbal medicines that they use

chronically. After collecting and analyzing the data of the present study, an informative folder was prepared (Figure 1 -Supplementary Material) to be distributed to research participants and other interested. The purpose of the folder is to disseminate data on Drug Interactions - especially those involving synthetic drugs used by elderly people - warning these people about these interactions, not only in the face of case reports presented by them, but also based on scientific studies found in the literature, demonstrating the relevance of communicating the use of PBNPs for pharmacovigilance and population health.

CONCLUSION

The reports made by the elderly can largely contribute to ethnopharmacological and pharmacovigilance studies due to the rich range of information contained in popular knowledge among this population, which frequently uses synthetic drugs and is exposed to different types of Mis important comparisons involving reported and scientific data could be made from the interviews, indicating that four of the seven plants reported possibly showed interactions with synthetic drugs, converging with information from the scientific literature. In addition, the possible IMs presented here may have been the result of the action of several PBNPs mentioned above on the enzyme complex cytochrome P450 - the main responsible for metabolizing drugs in the liver - which can cause unexpected adverse effects, such as inhibiting the action of drugs.

This work contributes to a better understanding that “natural medicine” can also be harmful in many cases. Although it is feasible to compare information from some plants and their respective studies, some of them have little or no knowledge recorded in the consulted databases, which makes the ability to understand and disseminate such interactions even more difficult. Thus, it is important for the patient to share information about the therapeutic use of PBNPs with the physician and pharmacist to receive the most appropriate prescription and necessary guidance, reducing the chances of DIs.

We also emphasize the need for more in-depth studies on the possible actions and interactions of plants, both in the context of interactions with synthetics and the complexity of polypharmacy; it was shown that part of the population uses phytotherapy as a complementary treatment to cure diseases. In addition, ADEs are considered a serious public health problem, as they cause a negative impact in several areas: clinical, humanistic and economic.

In this way, combining ethnopharmacological studies - based on field work - with constant data in the scientific literature can contribute to reflections on the risk in the use of medicinal plants, plant drugs and herbal medicines in urban contexts. In addition, they can help in this public health problem, reducing morbidity and mortality among patients, and consequently mitigating expenses in health systems.

AUTHORS’ CONTRIBUTIONS

The authors equally contributed to the manuscript.

DECLARATION OF CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

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SUPPLEMENTARY MATERIAL

Table S1. Reports of Drug Interactions between plant-based natural herbal products with synthetic drugs, herbal medicines and other substances or products, presented by users of the Centro de Convivência Municipal da Pessoa Idosa (CCMI) in Diadema, SP/Brazil

Medicinal plant	Drug Interaction Report
God's hand *Tithonia diversifolia* (Hemsl.) A.Gray	The case happened to the interviewee's brother, NMCM. He was using the plant to control diabetes, once a day, for 4 days. According to the interviewee, the right thing was to drink 1 cup of 200 ml, once a day, but her brother took it several times a day and began to lose weight continuously: "He started to lose weight, lose weight... low blood sugar and started feeling sick... he had to stay in hospital for a week because of that". He said he had the plant in his own backyard, where he collected it to make the recipe for him. Regarding the synthetic-Metformin-, she said that her brother used the dose on the label or prescribed by the doctor, and had been using these drugs for more than 20 years for diabetes.
Yacon *Smallanthus sonchifolius* (Poepp.) H.Rob.	The case happened with a friend of the interviewee, RTI. He said that he used this root to control diabetes, eating small, raw pieces: "There is no right dose, you eat the pieces, but it can't be too much"; and then indicated to her friend, who was using insulin (injectable): "But with her, she ate once and it had the opposite effect, worsening diabetes... She had to go to the hospital".
Jucá *Libidibia ferrea* (Mart. ex Tul.) LPQueiroz	Interviewee ML used her sister's prescription for 3 months, who said it was good for controlling diabetes. According to her, she left the seed cut in 4 pieces to soak for a day in 1L of water, with that a "black broth" came out, which she ingested. From the 3rd day of use, she started to have a lot of evacuation, in a severe way: "I had loose bowels, I had so much, but so much intestinal colic, that I thought I was going to die". However, she did not seek an emergency room, and continued to take the "medicine". She said that afterwards she didn't feel sick like that anymore, but that sometimes she released her bowels lightly. Regarding the synthetic-Losartan-, she said she used the dose prescribed by the doctor. She had been using these drugs for over 5 years.
Chilean Boldo *Peumus boldus* Molina	The interviewee NB reported having taken Chilean boldo tea while using the drugs Simvastatin, Aspirin®, Captopril and "Grandma's Syrup"; and after drinking the tea, she vomited: "I vomited after drinking the boldo tea, but I don't know if it was because of the plant or the syrup that gave me this". According to the participant, she had been using these synthetics for more than 5 years, ingesting the dose indicated on the leaflet or prescribed by the doctor.
Clove - *Syzygium aromaticum* (L.)	Interviewee MAS said that she was using cloves with water at room temperature, as a friend said it was good for controlling high blood pressure. According to her, it had been a long time since the pressure got out of control to the point of going to the emergency room, but she did not associate the fact that she felt sick with the consumption of cloves. "It had been a long time since I went to the emergency room because of the increased pressure". However, when asked if this event occurred during the time she was using clove water, she said yes. Regarding synthetics, she said that she used the dose on the label or prescribed by the doctor, and that she had been using these drugs for about 4 years.

Table S1. continued

Hibiscus *hibiscus sabdariffa* L.	According to MB, the synthetic medication to control hypertension (Enalapril) was not having any effect, and after ingesting the tea of this plant together with the synthetic medication, it had the expected result, that is, it regulated the pressure that was high: “after I took the hibiscus tea, my blood pressure dropped back, and I stopped feeling that discomfort, you know?!”. Regarding synthetics, she said she used the dose on the package insert or prescribed by the doctor. She had been using these drugs for over 5 years.
Chamomile *Matricaria chamomilla* L.	After using chamomile herbal tea, CRN reported having felt the same symptoms of high blood pressure, a disease she treated with Losartan and Hydrochlorothiazide: “I had chest pain, my heart sped up, I was short of breath... symptoms of when blood pressure is high”; and according to her, this event lasted approximately 20 mi, until she had a little sugar water, which made her feel better. Regarding synthetics, she said she used the dose prescribed by the doctor, and had been using these drugs for more than 5 years.