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Phytosurveillance: evaluation of interactions and adverse reactions of herbal medicines on the market

Fitovigilância: avaliação das interações e reações adversas de fitoterápicos no mercado

Ana Paula da Silva Roxo[I,*]
Elizabeth Valverde Macedo[II]
Samanta Cardozo Mourão[III]
Thalita Gonçalves Barros[III]
Emeli Moura de Araújo[I]
Carlos Augusto de Freitas Peregrino[III]
Marcela Miranda Salles[IV]

[I] Universidade Federal Fluminense (UFF), Niterói, RJ, Brasil

[II] Laboratório Universitário Rodolpho Albino, Universidade Federal Fluminense (UFF), Niterói, RJ, Brasil

[III] Faculdade de Farmácia, Universidade Federal Fluminense (UFF), Niterói, RJ, Brasil

[IV] Hospital Universitário Antônio Pedro, Universidade Federal Fluminense (UFF), Niterói, RJ, Brasil

***** **E-mail:** anapaularoxo@id.uff.br

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ABSTRACT

Introduction: The use of medicinal plants as active plant pharmaceutical ingredients (APPIs) as well as the use of herbal medicines and their associations with other herbal medicines and synthetic active pharmaceutical ingredients (API) can result in interactions that affect the efficacy and safe use of these. The main means of reporting adverse drug reactions (ADR) is voluntary, which makes the identification and monitoring of these ADRs difficult and portrays the importance of pharmacovigilance in our country, highlighting the need to strengthen the culture of reporting adverse drug events (ADE). **Objective:** To analyze the occurrence of ADR related to the simultaneous use of five herbal medicines with other synthetics, describing possible synthetic APPI-API interactions. **Method:** A literature search was carried out on synthetic APPI-API interactions and their notifications of ADR by the main pharmacovigilance systems in the world. **Results:** The main interaction mechanisms between synthetic APPI-API involve the metabolism by enzymes of the CYP450 family or the action of efflux transporters such as P-gp. In addition, a large part of phytotherapeutic AEM may not be being notified, generating possible underreporting of this information in the world. **Conclusions:** On ADR containing APPI from *Ginkgo biloba*, *Hypericum perforatum*, *Matricaria recutita*, *Allium sativum* and *Zingiber officinale*, 7,571 were reported worldwide, classified by continent, in the period 1971 to August 2021, as well as the list of plant species on the list of RENISUS that have reported effects on CYP enzymes (1A2, 2C9, 2C19, 2D6 and 3A4), levels of GSH, UGT and P-gp activity.

KEYWORDS: Health Surveillance; Phytosurveillance; Adverse Reactions; Herbal Medicines

RESUMO

Introdução: O uso de plantas medicinais como insumos farmacêuticos ativos vegetais (IFAV), bem como o uso de fitoterápicos e suas associações com outros medicamentos fitoterápicos e os insumos farmacêuticos ativos (IFA) sintéticos, pode resultar em interações que afetem a eficácia e o uso seguro desses. O principal meio de notificações de reação adversa a medicamento (RAM) é a voluntária, o que dificulta a identificação e o monitoramento dessas RAM e retrata a importância da farmacovigilância em nosso país, realçando a necessidade de fortalecimento da cultura de notificação de eventos adversos a medicamentos (EAM). **Objetivo:** Analisar a ocorrência de RAM relacionada ao uso simultâneo de cinco fitoterápicos a outros sintéticos, descrevendo as possíveis interações IFAV-IFA sintéticos. **Método:** Foi realizada pesquisa bibliográfica sobre as interações IFAV-IFA sintéticos e suas notificações de RAM pelos principais sistemas de farmacovigilância do mundo. **Resultados:** Os principais mecanismos de interação entre IFAV-IFA sintéticos envolvem a metabolização pelas enzimas da família CYP450 ou a ação de transportadores de efluxo como a gp-P. Além disso, grande parte dos EAM fitoterápicos podem não estar sendo notificados, gerando possível subnotificação dessas informações no mundo. **Conclusões:** Sobre RAM contendo IFAV de *Ginkgo biloba*, *Hypericum perforatum*, *Matricaria recutita*, *Allium sativum* e *Zingiber officinale*, foram relatados 7.571 no mundo, classificados por continente, no período de 1971 a agosto de 2021, bem como lista de espécies vegetais da lista do Renisus que apresentam efeitos relatados nas enzimas CYP (1A2, 2C9, 2C19, 2D6 e 3A4), níveis de GSH, UGT e atividade da gp-P.

PALAVRAS-CHAVE: Vigilância Sanitária; Fitovigilância; Reações Adversas; Fitoterápicos

INTRODUCTION

The increase in the consumption of herbal medicines is a global phenomenon. According to the World Health Organization (WHO), the world market for plant-based raw materials is around billions of dollars a year and, by 2050, it is estimated to reach 5 trillion dollars[1].

Phytotherapics contain active plant pharmaceutical ingredients (APPIs) and, when ingested, they are metabolized by the body and, if used with other drugs of synthetic origin, there may be some interactions between them that cause adverse drug reactions (ADRs), with different degrees of severity[2].

The denomination "herbal medicines" is a large category subdivided into two regulatory classes, called herbal medicines (HM) and traditional herbal product (THP). The first has its safety and efficacy based on clinical evidence. The safety and effectiveness of THP are based on data on safe and effective use published in the technical-scientific literature[3].

Herbal medicines make up the basic component of the Brazilian National Essential Medicines List (Rename) and there are 12 herbal medicines financed with resources from the Unified Health System (SUS)[4]. The Ministry of Health pointed out that more herbal medicines should be made available to the population by the SUS, as part of the objectives of the National Policy on Integrative and Complementary Practices (PNPIC), which led, in 2008, to the creation of the list of medicinal plants of interest to the SUS (National List of Medicinal plants of interest to SUS, Renisus), which contains 71 plant species[5,6].

Herbal medicine interactions

Cytochrome P450 (CYP) family enzymes are responsible for metabolizing almost 80% of drugs and for the action of P-glycoprotein (P-gp)[1,7].

Herbal medicines and active pharmaceutical ingredients (APIs), which are synthetic, can interact, and pharmacokinetic interactions have greater clinical importance when they change parameters such as maximum plasma concentration (C_{Max}), the area under the curve (AUC) showing the drug absorption rate after the first administered dose or the elimination half-life ($t_{1/2}$)[8].

The main CYP enzymes are: CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 and, when their inhibition occurs, there is a prolongation of the drug concentration in the body[9].

P-gp is an efflux transporter that acts in the transport and excretion of xenobiotics and has a significant role in the absorption of oral drugs and in the decrease of drug bioavailability. If this transporter is inhibited, toxic blood concentrations of drugs can occur. But, if by induction, it would result in a decrease in the effectiveness of synthetic drugs, leading to therapeutic failure[1].

Some widely used herbal medicines interact with synthetic drugs, such as those containing drugs or derivatives of: *Hypericum perforatum* L. (St. John's wort), *Ginkgo biloba L.* (ginkgo), *Zingiber officinale* Rosc (ginger), *Panax ginseng* CA Meyer (ginseng) e *Allium sativum* L. (garlic)[10].

An *in vitro* study analyzed the interactions of CYP3A4 and CYP2D6 enzymes with the standardized extract of nine medicinal plants and their chemical markers: *Bauhinia forficata* (quercetin 2%), *Cecropia glaziovii* (chlorogenic acid 0.11%), *Cimicifuga racemosa* (black cohosh triterpene glycosides 0.77%), *Cynara scolymus* (chlorogenic acid 0.5%), *Echinacea* sp. (tannins 1.62%), *Ginkgo biloba* (flavonoid glycosides 25.82%), *Glycine max* (isoflavone 40.5%), *Ilex paraguariensis* (chlorogenic acid 6.75%), and *Matricaria recutita* (flavonoids 0.16%). The drugs midazolam and metoprolol, which are substrates of CYP3A4 and CYP2D6 enzymes, were used. All extracts inhibited CYP3A4 activity, except for *Glycine max*. The *Cecropia glaziovii* extract showed the most relevant inhibitory effects of CYP3A4 and CYP2D6 activity, whereas that of *Ilex paraguariensis* inhibited CYP3A4 activity[11].

Pharmacovigilance of herbal medicines

In 2003, WHO proposed the inclusion of medicinal plants, blood and biological products, medicinal devices and vaccines to the International Pharmacovigilance System in the document called "Guidelines on Monitoring and Pharmacovigilance of Medicinal Plants"[12].

Pharmacovigilance is the science and activities related to the identification, assessment, understanding, and prevention of adverse events or any problems related to drugs[13], while phytosurveillance is the pharmacovigilance of products that contain raw material of plant origin[12].

The Brazilian National Health Surveillance Agency (Anvisa) uses two computerized systems for the notification of AE, Notivisa and VigiMed. The first one receives notifications of adverse event (AE) and technical complaint (TC) incidents related to the use of products and services under health surveillance and VigiMed receives notifications related to adverse drug events (ADE) and vaccines[14].

The main means of adverse drug reaction (ADR) notifications is voluntary; thus, underreporting becomes a limitation in the generation of data on ADR rates and frequencies. According to Anvisa, it is estimated that only 5% to 10% of ADRs are notified[15].

The WHO defines ADR as any harmful and unwanted reaction that occurs after the administration of a drug, in doses commonly used by man, to prevent, diagnose, and treat a disease or to modify some biological function[16] The ADE, on the other hand, has a broader meaning about drug exposure and is, therefore, any undesirable medical occurrence in a patient to whom a drug has been administered, without necessarily having a causal relationship with the treatment, and may be any unfavorable and unintentional sign, symptom, or disease temporally associated with the use of the drug[17].

In April 2015, the WHO launched the application VigiAccess, an electronic tool that allows access to and consultation of the worldwide database of suspected ADRs reports - VigiBase, developed and managed by *Uppsalla Monitoring Center* (UMC), which carries out international monitoring of ADE notifications by the pharmacovigilance sectors of its member states[18].

Developed countries are responsible for most reports of suspected ADRs, as they consume more drugs and have better infrastructure to monitor their safety. The number of reports received by VigiBase from June 2019 to June 2020 was almost 23 million at the end of the year. The number of individual case reports from low- and middle-income countries was 3,156,136[19].

The present study aimed to analyze the occurrence of ADR related to the simultaneous use of five HM: *Ginkgo biloba*, *Hypericum perforatum*, *Matricaria recutita*, *Allium sativum* e *Zingiber officinale,* with other synthetic drugs, describing the possible interactions between synthetic APPI-APIs.

METHOD

The present work is an integrative literature review that was carried out in two stages.

First stage of research

For data collection, electronic platforms were used: Scientific Electronic Library (SciELO), National Center for Biotechnology Information (NCBI/PubMed), Virtual Health Library (BVS), and Embase (Elsevier). The health sciences descriptors (DeCS) chosen were: farmacovigilância (*pharmacovigilance*); medicamentos fitoterápicos *(herbal medicine*); interações ervas-drogas (*herb-drug interactions*); efeitos adversos (*adverse effects*). The search was conducted using the combination of keywords, with the Boolean operator AND, to match the terms. In Embase, in the quick search field, terms were pasted and searched individually. Then AND was added and then COMBINE to search for terms together. The combination of terms was: Herbal Medicine AND Pharmacovigilance; Herb-Drug Interactions AND Adverse effects.

Other sources used were: *Revista Vigilância Sanitária em Debate: Sociedade, Ciência & Tecnologia (Visa em Debate)*, with the objective of researching articles that reported the notification rate in the country, since, when searching on the Anvisa website, specifically in the Alerts Database (http://antigo.anvisa.gov.br/alertas), it was not possible to find data on notifications made through Notivisa and VigiMed. Rules related to pharmacovigilance were also searched on the Agency's website.

The criteria for inclusion of references for the development of this study were: articles published in the format of scientific articles; articles published in English and Portuguese; articles that addressed herbal medicines, drug interaction, and ADE as the main subject. The exclusion criteria were: articles with abstracts that did not address the intended topic; theses, conference abstracts, and papers presented at congresses.

Second stage of research

After reading the articles obtained in the first stage, the plant species were selected: *Ginkgo biloba*; *Hypericum perforatum*, *Matricaria recutita*, *Allium sativum*, and *Zingiber officinale*, *because they were present in most of the selected articles. The SciELO database was not used in the second stage of the research due to the low number of articles found in the first.* The combination of keywords was: *Allium sativum* AND *Herb-Drug Interactions; Hypericum perforatum* AND *Herb-Drug Interactions; Zingiber officinale* AND *Herb-Drug Interactions; Ginkgo biloba* AND *Herb-Drug Interactions; Matricaria recutita* AND *Herb-Drug Interactions*

The WHO website was also used to obtain informative materials on pharmacovigilance, in addition to research in the VigiAccess application (http://www.vigiaccess.org)[18], to obtain reports of ADRs in the world, of the aforementioned plant species, for further analysis of these notifications. On the European Medicines Agency (EMA) website (https://www.ema.europa.eu/en/human-regulatory/herbal-medicinal-products), monographs of the plant species identified in the first stage were searched.

The search period in the first stage of the research was between April 1st and 3rd, 2021. The second stage was carried out on August 1st, 2021.

RESULTS AND DISCUSSION

The number of articles found in the electronic databases and which were described in the methodology of this research is shown in Table 1.

At the end of the searches, 94 references were selected, of which 15 articles were excluded because they were repeated. Soon after, a complete reading of the 79 articles was carried out, of which 36 articles were selected.

Studies evaluating interactions involving herbal medicines

Allium sativum L.

EMA, in its monograph of plant species, classifies *Allium sativum* (*A. sativum*), known as garlic, as a traditional herbal medicine for use in the specified indications based solely on long-standing use, being indicated for use as an adjunct in the prevention of atherosclerosis and for the relief of symptoms of the common cold[20].

Garlic can inhibit or induce the CYP450 enzymes of the hepatic system and P-gp in the intestine. Aqueous garlic extract (0-200 µg/mL) was tested *in vitro*, in human hepatocyte cells, against the enzymatic activity of CYP2C9 and CYP3A4. In the end, inhibition of CYP2C9 was observed and no effect on CYP3A4[21].

An *in vitro* study showed pharmacokinetic interactions between indinavir and Viral Choice® capsules containing 50 mg of garlic and showed that garlic was able to decrease the absorption of

Table 1. Search strategy and number of articles found in the first and second stages of the research.

1st part of the research	SciELO	PubMed	VHL	Embase
Herbal medicine AND *Pharmacovigilance*	5	195	243	736
Herb-Drug Interactions AND *Adverse effects*	10	1,055	2,075	506
2nd part of the research		**PubMed**	**VHL**	**Embase**
Allium sativum AND *Herb-Drug Interactions*	-	118	88	180
Hypericum perforatum AND *Herb-Drug Interactions*	-	185	329	325
Zingiber officinale AND *Herb-Drug Interactions*	-	71	46	115
Ginkgo biloba AND *Herb-Drug Interactions*	-	144	199	340
Matricaria recutita AND *Herb-Drug Interactions*	-	5	3	10

Source: Elaborated by the authors, 2021.
VHL: Virtual Health Library.

indinavir due to the decrease in its bioavailability by induction of P-gp[22]. Another study with garlic extracts in humans showed a decrease in the concentrations of drugs that are transported by P-gp, such as colchicine, digoxin, doxorubicin, quinidine, rosuvastatin, tacrolimus, and verapamil. Therefore, these should not be combined with garlic supplements as interactions may occur[23].

In vitro studies suggest that garlic inhibits CYP2C9, CYP3A, and CYP2D6. Warfarin when used along with garlic supplements can increase bleeding time and potentiate the action of warfarin. Blood clotting time has been reported to double in patients who take garlic supplements along with warfarin[24].

in vivo studies showed that administration of 5 mL/kg of raw garlic juice resulted in stomach injury that led to the death of rats. Chronic administration of 50 mg of garlic powder per day resulted in inhibition of spermatogenesis in rats. Studies in rats have shown that garlic powder, containing allicin at a concentration of 200 mg/mL, can lead to significant cell damage in the liver of rats. Garlic consumption, at 250, 500, and 1000 mg/kg/day, led to acute deformities in the liver and lung tissue of rats. Also, the daily intake of 1,000 mg/kg resulted in morphological deformities in the liver of rats, seen by microscope. On the other hand, garlic bulb extract, at doses of 300 and 600 mg for 21 days, led to growth retardation in male and female rats[25].

Hypericum perforatum L.

Hypericum perforatum L. (*H. perforatum*), also known as St. John's wort or hypericum, it is used as an adjunct in the short-term treatment of mild to moderate depressive episodes[26].

A phase I clinical trial involving 12 healthy volunteers was carried out to investigate the interaction of the drug rifampicin with hypericum capsules (Jarsin®, Casella Med, Germany). These received different doses of hypericum, varying the dosage and duration of treatment, all orally. At the end of the trial, five of the six female participants developed dermatological and neurological symptoms after sun exposure[27].

While another controlled, randomized, crossover, and placebo study was conducted with 12 healthy participants using the 300 mg dose of St. John's wort (Li 160, Jarsin 300 mg, Klosterfrau, Berlim, Germany; John's wort dry extract 3-6:1, the extraction solvent being 80% methanol and the hyperforin range of 2-6%). The study showed that there was a 50% decrease in AUC, elimination $T_{1/2,}$ absorption and an increase in oxycodone elimination when concomitant use with hypericum occurred[28].

Hypericum can affect the plasma concentration (PC) of different drugs that are metabolized by the CYP450 family, as it induces CYP3A4, CYP2E1, and CYP2C19, and also by P-gp. Its main interactions are with immunosuppressants, cyclosporine, as it reduces PC, which can lead to transplant rejection; reduced effectiveness of oral contraceptives (tibolone), reduced PC of antiretroviral drugs such as indinavir, nevirapine and anticancers such as imatinib and irinotecan[29].

A single-center randomized clinical trial using 300 mg of St. John's wort showed that hypericum may enhance the antiplatelet effect of clopidogrel. Because of this, hypericum may potentiate the action of the drug in patients with a low response to it, when the therapy is combined with hypericum[30].

Warfarin metabolism generates two enantiomers, R-warfarin, which is mainly metabolized by CYP1A2 and 3A4, and the more potent S-warfarin, which is metabolized by CYP2C19A. Clinical trial showed that hypericum induces the apparent elimination of S and R-warfarin, leading to a significant reduction in the racemic index and pharmacological effect of warfarin and, consequently, to an increase in prothrombin time[31]

Zingiber officinale Roscoe

In the European Union (EU), medicinal products based on *Zingiber officinale* Roscoe (*R. officinale*), better known as ginger, are used for the prevention of nausea and vomiting in motion sickness and are based on their well-established use. In cases of nausea symptoms, mild complaints that affect the stomach or intestines, the treatment is based on its traditional use. Regarding the use of powdered ginger, some ADEs were identified with a

single dose, such as: abdominal discomfort (using 1,500 mg) and eructation, belching (using 1,000 mg). When it involved more than a dose of 1,050 mg, for a period of three weeks, dyspepsia (heartburn) and nausea were observed[32].

Ginger powder significantly inhibits CYP3A4, CYP2C9 and P-gp activities *in vitro*, at concentrations of 4.0, 1.0 and 5.1 g/mL which can result in reduced effectiveness and increased toxicity of drugs that use these pathways[33]. Another *in vitro* using human liver microsomes evaluated the interaction of aqueous-ethanolic ginger extract (0.05-5.00 µg/mL) on drug metabolism mediated by the CYP system. The selective inhibitors used were: furafylline (CYP1A2), methoxalene (CYP2C9), sulfaphenazole (CYP2C9), ticlopidine (CYP2C19), quinidine (CYP2D6), and ketoconazole (CYP3A4). At the end of the study, hypericum inhibited CYP2C19[34].

In a study carried out with 20 healthy volunteers, 5 g of dry ginger powder were administered daily, with the concomitant use of warfarin. At the end, a significant reduction in platelet aggregation was observed in all volunteers. Ginger inhibits the synthesis of thromboxane A2 (TxA_2) and stimulates the synthesis of prostacyclins, which negatively affect platelet aggregation. Prolonged and continuous use of ginger in large amounts may increase the risk of bleeding in patients on chronic warfarin therapy[35].

An animal study evaluated the possible interactions between dry ginger powder and acetaminophen, and observed that the antinociceptive effect of acetaminophen increased, improving cognitive disturbance linked to pain perception[29].

Matricaria recutita L.

Matricaria recutita L. (*M. recutita*) of the Asteraceae family, better known as chamomile, has therapeutic action for minor injuries, cough, cold, and for mouth, throat, skin, and gastrointestinal disorders. The plant has as main constituent substances that give its characteristic: essential oil (α-bisabolol, bisabolol oxide, and chamazulene), flavonoids (apigenin-7-glycoside apigenin and luteolin), sesquiterpene lactones (matricin), coumarins, and phenolic acids[36].

Oral administration of 250 mg/kg of apigenin can increase AUC and prolong the maximum time (Tmax) of the drug venlafaxine, used in depression, when there is concomitant use of these drugs. When used with raloxifene for post-menopausal osteoporosis, it may increase its bioavailability and decrease its first-pass metabolism. In addition, it acted synergistically with ceftazidime, reversing the resistance of the bacterium *Enterobacter cloacae* to cephalosporin. Finally, apigenin improves the efficacy of aspirin in inhibiting platelet aggregation, partially supplying the TxA_2pathway *ex vivo*, showing that apigenin has the potential to interact with other drugs[37].

A study conducted in Israel with 299 patients showed the potential for interaction of ginger tea with CYP3A4, which may have led to the elevation and toxicity of cyclosporine, an immunosuppressant, due to the inhibition of CYP3A4, in a patient[38].

In a study *in vivo* with male rats weighing between 180 and 220 g, the ability of paclitaxel, used in cancer treatment, to interact with apigenin (10, 20, and 40 mg/kg) for 15 consecutive days was evaluated. There was an increase in AUC, $t_{1/2}$, and in $C_{Máx}$ in a dose-dependent manner. Thus, it was possible to observe an increase in the bioavailability of paclitaxel co-administered with apigenin due to the inhibition of CYP3A4 and the P-gp efflux pump in the intestinal mucosa of rats[39].

Ginkgo biloba L.

Two substances that are part of the *Ginkgo biloba* (Gb) leaf are flavonoids and terpenolactones. Flavonoids are represented by 20 compounds, including heteroside derivatives of flavonoids, with free radical scavenging activity, and biflavonols. Terpenolactones (diterpenes: ginkgolides A, B, C, J) are related to the ability to inhibit platelet aggregation factor[40].

An *in vitro* study using rat liver microsome showed that the Gb extract (GbE 761, contained 24% flavonoids and 6% terpenolactones) significantly increased the conversion of clopidogrel to its active metabolite. The doses of ginkgo used during the study were: 4 mg/kg, 20 mg/kg, and 100 mg/kg. At the end of the experiment, there was a significant decrease in Cmax and drug AUC due to P-gp inhibition by ginkgo[41].

The *in vitro* study study with human hepatocytes cells using the hydrolyzed extract of Gb (10-100 mM in terpenolactone concentration) caused dose-dependent inhibition of 6α-hydroxylation of Gb by inhibiting CYP2C8[42]. In humans, paclitaxel is primarily metabolized by 6α-hydroxylation, mediated by the CYP2C8 enzyme.

An *in vitro study,* which lasted 25 days, evaluated the extract of ginkgo (Seredrin®, Bioplanta Arzneimittel GmbH, lot no. 3090103) in the inhibition of CYP3A4 and P-gp. Enzyme activity was determined by testosterone 6-β hydroxylation formation and ketoconazole applied as a positive control inhibitor for CYP3A4. On the other hand, inhibition of P-gp transport was quantified by intracellular accumulation of digoxin in the small intestine and verapamil applied as a positive control inhibitor for P-gp. At the end of the experiment, ginkgo inhibited CYP3A4 and was also a potent inhibitor of P-gp in the intracellular transport of digoxin[43].

The *in vivo* study using rats evaluated the pharmacokinetic interaction between the aqueous extract of Gb and carbamazepine. Two groups of animals were used, each containing six rats. At the end of the experiment, there was a significant decrease in AUC and Cmax in both groups, showing a reduction in bioavailability and an increase in the rate of elimination of carbamazepine by the body[44].

A study carried out with ten healthy male volunteers aimed to test the influence of repeated oral administration of GbE on CYP2C9 and CYP3A4 enzymes. During the study, CYP2C9 enzyme probes with tolbutamide (125 mg) and CYP3A4 enzyme probe with midazolam (8 mg) were used orally, before and after the ingestion of GbE 761 tablets (360 mg/day), with its extracts

standardized in 24% flavonoids and 6% terpenolactones, for 28 days. Volunteers received 75 g of glucose after dosing with antidiabetic tolbutamide. Drug PCs and glucose levels were measured. The AUC for tolbutamide after ingestion of GbE was 16% lower than before ingestion of GbE. Treatment with GbE tended to minimize the effect of blood glucose lowering by the action of tolbutamide in the blood. AUC for midazolam was increased by 25% by ingestion of GbE and oral release was reduced by 26%[45].

Gb can inhibit CYP3A4 and induce CYP2B6, CYP2C19, and CYP3A4. For example, a 47-year-old patient infected with the human immunodeficiency virus (HIV) and who received antiretroviral therapy with efavirenz for 10 years had treatment failure. In this case, it is believed that terpenoids present in Gb may have caused the induction of CYP3A4 or P-gp. Therefore, the decrease in plasma levels of efavirenz, in this particular clinical case, could also have been caused by the induction of P-gp[46].

A case of intracerebral hemorrhage involved a 78-year-old patient, after the concomitant use of warfarin and an herbal medicine based on ginkgo. Another example of a possible interaction involved a 33-year-old woman who developed bilateral subdural hematomas and had a prolonged bleeding time, which normalized when ginkgo stopped being consumed[47].

The use of ginkgo and nifedipine, a calcium channel antagonist, may increase the frequency of ADE caused by the use of the drug nifedipine, such as headache, redness and ankle swelling, fainting, and tachycardia. In an open clinical trial, the use of ginkgo extract caused an increase in nifedipine PC of approximately 29%, possibly due to the interaction of ginkgo with nifedipine and which led to the inhibition of the CYP3A4 enzyme[48].

Herbal medicine reports

On the website of *Visa em Debate* magazine, two articles were found that dealt with the number of reports received by Anvisa. The first showed that, from January 1999 to March 2009, 20 thousand notifications were made, with ADE. Of the 20 thousand notifications registered, 165 were of AE related to medicinal plants and/or herbal medicines. However, it was analyzed and identified that some notifications contained more than one ADE reported, in a single notification, which equates to 77 of the notifications with more than one ADE reported. Of the 165 notifications, 71 (43%) were direct suspected cases; six (4%) were indirect suspects, and 88 (53%) reported more than one ADR in this period. The severity of ADE reported was 20% as severe and three deaths[12].

The second collected data from 2008 to 2012, when 50,824 reports referring to medicines were registered. Among these, 399 were products with one or more plants in their composition and were reported as medicines, being excluded from the study those that did not have a description of the product, the active substance, or contained only isolated active principles. In the 399 reports, ten (2.5%) were from AE and 389 (97.5%) from TC. The other categories of medications had 27,082 (54.0%) TC and 23,343 (46.0%) AE[49].

Underreporting

An explanation may be linked to cultural issues, as people see these products as harmless and that, because they are natural, they are good. This, in a way, generates a false security in relation to the correct use of these. In addition, the low number of AE notifications caused by them does not generate enough information on the subject, which makes it even more difficult to apply an effective pharmacovigilance system for these products.

Underreporting implies a potential increase in costs for the health system, as they can lead to serious ADRs. This could be avoided if the reporting culture were implemented among health professionals and in the population applicable to the use of any medication. Therefore, it is urgent to discuss these issues, in order to increase awareness of the safe and rational use of medicines, whether herbal or not.

Table 2 shows the notifications received from plant species *G. biloba*, *H. perforatum*; *M. recutita*, *A. sativum*, *Z. officinale*, by the UMC, related to the use and reports of ADRs according to age.

The most frequent diseases associated with the use of herbal medicines were: stroke, followed by cancer, heart disease, and arthritis. A possible explanation for the demand for herbal medicines would be that the treatments of these diseases are challenging, and cure and complete recovery are not guaranteed, so there is hope coming from nature[50].

Despite the very low rates of ADR reports, the commercialization of herbal products has been growing, which suggests that a large part of herbal ADEs may not be being notified, generating possible underreporting of this information worldwide. Table 3 shows that, from 1971 to 2021, there were only 4,643 reports of ADRs involving *G. biloba* in all countries that are part of the WHO, which implies that, in the world, in the period of 30 years, only 4,643 ADRs were reported involving the use of G. *biloba*. The same happens with *H. perforatum* L. (2,347 reports), *M. recutita* L. (127 reports), *A. sativum* L. (220 reports), and *Z. officinale* Roscoe (237 reports).

As seen in Table 3, Europe is the continent that most reports (4,523 reports in total), converging to the same profile seen previously in developed countries, which is the greater consumption of medicines, as they have greater purchasing power and infrastructure to monitor their safety. With the lack of relationship between ADEs and the use of such products, there is not enough data for these correlations, which causes a delay in the pharmacovigilance system for these products.

In Brazil, the Sentinel Network is largely responsible for the expressive numbers of notifications of incidents, AE, and TC related to the use of products and services under sanitary surveillance. Through it, in 2016, 184,331 (43%) of the total of 426,847 ADE notifications were made. The remaining reports were made

Table 2. Reports of adverse drug reactions (ADRs) in relation to age, involving plant species carried out in the world from 1971 to August 2021.

Age	*G. biloba*		*H. perforatum*		*M. recutia*		*A. sativum*		*Z. officinale*	
	R	%	R	%	R	%	R	%	R	%
0-27 days	17	0	5	0	1	1	1	0	0	0
28 days to 23 months	2	0	2	0	32	25	2	1	0	0
2 - 11 years	8	0	7	0	5	4	10	5	11	5
12 -17 years	19	0	33	1	0	0	4	2	9	4
18 - 44 years	371	8	633	27	20	16	45	20	55	23
45 - 64 years	1,221	26	589	25	15	12	58	26	69	29
65 - 74 years	918	20	144	6	9	7	28	13	30	13
≥ 75 years	1,182	25	102	4	8	6	25	11	27	11
Unknown	905	20	832	35	37	29	47	21	36	15
Total	4,643		2,344		127		220		237	

Source: VigiAccess - Word Health Organization (WHO), 2021.
R: reports; G.: *Ginkgo*; H.: *Hypericum*, M.: *Matricaria*; A.: *Allium*; Z.: *Zingiber*.

Table 3. Reports of adverse drug reactions (ADRs) by continent involving plant species from 1971 to August 2021, worldwide.

Species	Africa		America		Asia		Europ		Oceania		Total
	R	%	R	%	R	%	R	%	R	%	
G. biloba	37	1	190	4	1,940	42	2,403	52	73	2	4,643
H. perforatum	4	0	191	8	131	6	1,911	81	110	5	2,347
M. recutia	9	7	14	11	6	5	96	76	2	2	127
A. sativum	43	20	56	25	12	5	68	31	41	19	220
Z. officinale	26	11	66	28	58	24	45	19	42	18	237
Total	119		517		2,147		4,523		267		

Source: VigiAccess - Word Health Organization (WHO), 2021.
R: reports; G.: *Ginkgo*; H.: *Hypericum*, M.: *Matricaria*; A.: *Allium*; Z.: *Zingiber*.

by health professionals (31,844), by companies (44,884), by citizens (16), by health care establishments (2,782), and other notifying categories (162,990)[51] This demonstrates the important role that sentinel hospitals play in notifications, with almost half of notifications made in 2016. It also emphasizes the importance of health professionals in the notification process through sentinel hospitals, since they are most responsible for notifications within the hospital environment.

The probability of occurrence of ADE resulting from interactions of herbal medicines with medicines containing synthetic APIs consumed by the elderly population is significant, as these individuals use polypharmacy. Understanding and predicting the possible pharmacokinetic and pharmacodynamic interactions and ADRs is extremely important to avoid and prevent these or even therapeutic failure[52]. Table 4 shows the most frequent ADRs reported by the WHO for some plant species.

Some factors may contribute to the underreporting of herbal medicines' ADRs, among them the non-reporting of the use of herbal medicines by the user to the doctor, as they do not consider herbal medicines as medicines[53].

A Brazilian study investigated the use of home remedies by users of Primary Health Care (PHC) in the city of Blumenau, Santa Catarina, through a questionnaire answered by 701 people. From this questionnaire, 151 people (21.9%) used home remedies frequently, the most used being lemon balm, chamomile, mint, lemon, and boldo. The places where the plants were obtained were: 76 (51.0%) people took them in their backyard, 19 (12.8%) with friends, family, or neighbors, 14 (9.4%) bought them in pharmacies, and 36 (24.2%) in natural products market/store. Only four (2.7%) respondents reported obtaining plants at the health unit. Its main form of preparation was as tea (87.4%)[54].

PHC is the gateway to SUS. After the publication of the National Policy and Program of Medicinal Plants and Herbal Medicines (PNPMF) in 2006, an increase in the use of alternative therapeutic practices supported by policies within SUS was observed, in particular the use of medicinal plants and herbal medicines[55].

As for Renisus plants and their possible interactions with synthetic APIs with a low therapeutic index and chronic use, especially by the elderly population, the species on the list can

Table 4. Some reports of adverse drug reactions (ADRs) from plant species between the period 1971 to August 2021.

ADR	*G. biloba*	*H. perforatum*	*M. recutia*	*A. sativum*	*Z. officinale*
Nausea	318	142	4	10	15
Dyspepsia	176	31	-	9	19
Diarrhea	157	82	11	9	17
Constipation	55	12	2	4	2
Abdominal discomfort	115	84	5	3	18
Palpitations	83	56	4	4	4
Anxiety	27	72	1	3	1
Dyspnea	71	31	8	8	8
Tinnitus	87	8	-	1	2
Visual impairment	34	25	1	3	2
Fatigue	68	119	2	2	4
Drug interaction	65	115	4	13	13
Dizziness	569	121	4	8	6
Insomnia	83	56	-	4	6
↓ Therapeutic response	7	22	-	-	3
Headache	457	136	-	4	13
Hypotension	29	10	-	11	2
▫ Blood pressure	47	25	-	1	1
Arthralgia	30	20	-	-	3
Hepatitis	19	12	-	1	-
Jaundice	20	7	-	2	1
Pruritus	390	89	5	11	8
Hemorrhage	26	21	3	18	5
Hematuria	13	1	-	2	3
Intermenstrual bleeding	4	40	-	-	-
Acute kidney injury	10	3	-	2	1
Hypersensibility	47	31	9	2	5
Anaphylactic shock	6	3		-	2
Death	7	4	-	-	-

Source: VigiAccess - Word Health Organization (WHO), 2021.
ADR: adverse drug reaction; G.: *Ginkgo*; H.: *Hypericum*, M.: *Matricaria*; A.: *Allium*; Z.: *Zingiber*.

interfere with first-pass (CYP enzymes), second-pass (GSH and UGT), and on P-gp activity in the body[6]. Such interactions are summarized in Table 5.

As also seen in Table 5, approximately half of the medicinal plants contained in Renisus do not have pharmacokinetic data and most of the studies performed were carried out *in vitro*. In the scientific literature, there are few reports on synthetic APPI-API interactions between essential drugs prescribed in the SUS. In this context, it would be important to carry out more pharmacokinetic studies and more pharmacovigilance data to determine its clinical importance[6].

Interactions between synthetic APPI-APIs occur due to the complex characteristic present in herbal medicines that facilitates possible chemical interactions. These impact on pharmacological activity, blood levels, metabolism, or drug toxicity. An herbal medicine can contain more than 150 ingredients, which makes it difficult to identify what caused ADE and their interactions[56].

CONCLUSIONS

Given the underreporting of herbal ADRs, there is great concern about safety in relation to the interaction of synthetic APPI-APIs used in clinical practice, especially with drugs with low therapeutic indexes. These interactions can be pharmacokinetic and/or pharmacodynamic, leading to changes in elimination and toxicity to the drugs used by patients. The identification of synthetic APIs that interact with IFAVs has important implications for the development of new drugs, especially when they are

Table 5. Plant species from the National List of Medicinal plants of interest to SUS (Renisus) that have reported effects on CYP enzymes (1A2, 2C9, 2C19, 2D6 and 3A4), GSH and UGT levels, and P-gp activity.

Plant species	GSH	UGT	P-gp	1A2	2C9	2C19	2D6	2E1	3A4
Achillea millefolium	+		-						
Allium sativum	+	+	+	+	- /+	-	NE	-	- /NE
Aloe vera/Aloe barbadensis	- /+								
Anacardium occidentale	+								
Baccharis trimera	-								
Bauhinia forficata	-								
Bauhinia variegata	+								
Calendula officinalis	+								
Chamomilla recutita	+								-
Croton cajucara	+								
Curcuma longa	+	-	NE	+				NE	NE
Cynara scolymus	+/NE								
Eucalyptus globulus				-	-	-	-		-
Foeniculum vulgare	+								-
Glycine max	+			-				NE	
Ruta graveolens	+								
Harpagophytum procumbens				- /NE	-/NE	NE	-/NE		- /NE
Mentha piperita	+			--	-	-	-		-
Mentha pulegium	+								
Mikania glomerata	NE								
Momordica charantia	+			--				-	-
Phyllanthus amarus	-			-			-	-	-
Phyllanthus niruri	+								
Phyllanthus urinaria	+							-	
Psidium goiaba	+								
Punica granatum	+/-			-	-		-	-	-
Trifolium pratense				-	-	-	-		-
Uncaria tomentosa									-
Zingiber officinale	+/NE				-				-

Source: Mazzari and Prieto[6].
GSH: glutathione; UGT: glucuronidation; P-gp: P glycoprotein; (-): inhibition; (+): induction; NE: no effet; blank: no reports.

metabolized by CYP450 family enzymes or undergo the action of efflux transporters such as P-gp.

In many cases, patients think that herbal medicines, because they are natural products, are safe, not finding it necessary to mention them during the consultation with the health professional/prescriber, not even the doses. Because of this, it is quite likely that synthetic APPI-APIs interactions are significantly underreported and occur quite frequently and, in milder cases, are not even noticed. Thus, the constant updating of SUS users by health professionals can contribute positively to the perception of possible interactions between synthetic APPI-APIs, so that they can be notified to Anvisa.

About AMR containing APPI from *Ginkgo biloba*, *Hypericum perforatum*, *Matricaria recutita*, *Allium sativum*, and *Zingiber officinale*, 7,571 were reported worldwide, classified by continent, from 1971 to August 2021, as well as a list of plant species from the Renisus list that have reported effects on CYP enzymes (1A2, 2C9, 2C19, 2D6 and 3A4), GSH and UGT levels, and P-gp activity.

The notification of ADE should be encouraged in relation to all medicines and, especially, in relation to herbal medicines, since the idea that because they come from nature and do not harm must be deconstructed. The importance of sensitizing the population and health professionals that the use of herbal medicines

should be reported in consultations is also highlighted, as well as encouraging the practice of notification of ADE by citizens.

Therefore, ADE notification contributes to the prevention of future ADRs or any other drug-related problems, through the actions of those involved at different levels of the health system. Therefore, consultation and reading of the alerts published by Anvisa on its website should be encouraged by the entire population and health professionals.

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Author's Contributions

Roxo APS – Conception, planning (study design), acquisition, analysis, data interpretation, and writing of the work. Macedo EV - Conception, planning (study design), and writing of the work. Mourão SC, Barros TG, Araújo EM - Data interpretation and writing of the work. Peregrino CAF, Salles MM - Writing of the work. All authors approved the final version of the work.

Conflict of Interests

The authors inform that there is no potential conflict of interest with peers and institutions, politicians, or financial in this study.

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