

## MEDICINE-FOOD INTERACTIONS: INFORMATION GAPS IN BRAZILIAN PACKAGE INSERT.

INTERAÇÕES MEDICAMENTO-ALIMENTO: LACUNAS DE INFORMAÇÃO NAS BULAS BRASILEIRAS DE MEDICAMENTOS.

INTERACCIONES MEDICAMENTOS-ALIMENTOS: VACÍOS DE INFORMACIÓN EN LOS PROSPECTOS DE MEDICAMENTOS BRASILEÑOS.

### RESUMO

O uso simultâneo de medicamentos e alimentos pode interferir na cinética dos medicamentos, bem como na absorção e utilização de nutrientes. Analisou-se a informação sobre interações medicamento-alimento presente nas bulas dos medicamentos e a concordância entre essa informação e a literatura. Foram analisadas as bulas eletrônicas de medicamentos listados na Lista Nacional de Medicamentos Essenciais (RENAME). Realizou-se uma análise comparativa entre a informação contida na literatura e nas bulas destinadas a profissionais de saúde e pacientes. Dos 110 medicamentos, 65 (59,1%) apresentaram alguma interação com alimentos. Ao comparar a informação da literatura com as bulas dos profissionais de saúde, observou-se concordância em 6 (9,2%) bulas, concordância parcial em 22 (33,8%), nenhuma concordância em 22 (33,8%) e dados inexistentes em 15 (23,1%) bulas. Em relação às bulas dos medicamentos, houve concordância em 6 (9,2%), concordância parcial em 19 (29,2%), discordância em 17 (26,2%) e ausência de dados em 23 (35,4%). As interações farmacocinéticas foram as mais comuns. Observou-se alta frequência de ausência de informações relevantes sobre interação medicamento-alimento nas bulas, o que pode levar a uma maior exposição a riscos relacionados ao uso racional de medicamentos.

**Palavras-chave:** Bula de medicamentos; Interações Alimento-Medicamento; Interações medicamentosas; Alimentos; farmacocinética

### ABSTRACT

Simultaneous use of medicines and food may alter the kinetics of the medicines and the absorption and utilization of nutrients. This study analyzed information on medicine-food interactions in package leaflets and verified its consistency with the literature. The package leaflets of medicines listed on the National List of Essential Medicines (RENAME) were analyzed. Then, the information obtained in the literature was compared with that from the package leaflets intended for healthcare professionals and patients. Of the 110 medicines, 65 (59.1%) had some interaction with food. When comparing the information in the literature with the package leaflets of healthcare professionals, agreement occurred in 6 (9.2%), partial agreement in 22 (33.8%), no agreement in 22 (33.8%), and missing data in 15 (23.1%). Considering the package leaflets of the patients, agreement was observed in 6 (9.2%), partial agreement in 19 (29.2%), no agreement in 17 (26.2%), and missing data in 23 (35.4%). Pharmacokinetic interactions were the most common. Most package leaflets lacked relevant information on medicine-food interactions, potentially leading to greater exposure to risks related to the rational use of medicines.

**Keywords:** Medicine package leaflets. Food-medicine interactions. Medicine interactions. Foods. Pharmacokinetics.

### RESUMEN

El uso simultáneo de medicamentos y alimentos puede interferir en la cinética de los medicamentos, así como en la absorción y utilización de nutrientes. Se analizó la información sobre interacciones entre medicamentos y alimentos presente en los prospectos y si existía concordancia entre esta información y la bibliografía científica. Se analizaron los prospectos electrónicos de los medicamentos incluidos en la Lista Nacional de Medicamentos Esenciales (RENAME). Asimismo, se realizó un análisis comparativo entre la información contenida en la bibliografía y la presente en los prospectos dirigidos a profesionales sanitarios y a pacientes. De los 110 medicamentos analizados, 65 (59,1%) presentaron alguna interacción con alimentos. Al comparar la información de la bibliografía con la de los prospectos dirigidos a profesionales sanitarios, se observó concordancia en 6 (9,2%), concordancia parcial en 22 (33,8%), discordancia en 22 (33,8%) y ausencia de datos en 15 (23,1%) de los prospectos. En relación con los prospectos dirigidos a pacientes, se observó

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concordancia en 6 (9,2%), concordancia parcial en 19 (29,2%), discordancia en 17 (26,2%) y ausencia de datos en 23 (35,4%). Las interacciones farmacocinéticas fueron las más frecuentes. Se observó una alta frecuencia de ausencia de información relevante sobre la interacción entre medicamentos y alimentos en los prospectos, lo que puede conllevar una mayor exposición a riesgos relacionados con el uso racional de los medicamentos.

**Palabras clave:** Prospectos de Medicamentos; Interacciones Alimento-Droga; Interacciones Farmacológicas; Alimentos; Farmacocinética.

## INTRODUCTION

The medicine package insert is a legal health document that accompanies the medicine to inform its composition and important guidelines for use, such as dosage regimen, indication, contraindication and interactions (Fugita, Machado, Teixeira, 2014). The content of the package insert in Brazil is based on the information in the drug approval registers previously submitted to the National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária - ANVISA*), which is responsible for regulating, analyzing and approving them. The registration information is of a technical-scientific nature, derived from the results obtained in the development of a drug through clinical research. This characterizes the package insert as a descriptive document of the medicine, and it is also an institutionalized document, since its content has been regulated by rules established by government bodies over seven decades and is the result of the constitution of various actions/activities of different agents/actors who occupy the production chain of a medicine (Fugita, Machado, Teixeira, 2014).

The ANVISA, makes this document available in two forms: a package insert for the patient, with more accessible terms for the general population; and the electronic package insert for health professionals, which contains more scientific content and more technical information (ANVISA, 2021). In Brazil, the legislation that deals with specific matters

related to package inserts is the Resolution of the Collegiate Board (RDC) n°47/2009, which is the technical regulation that establishes the minimum requirements for the elaboration, harmonization, updating, publication and availability of package inserts for patients and health professionals (ANVISA, 2009). This legal framework has the objective of improving the form and content of package inserts for all registered and notified medicines sold in Brazil, aiming to guarantee access to safe and adequate information in favor of the rational use of medicines (ANVISA, 2009). Additionally, there is RDC No. 137/2003, which concerns the rule on warnings and precautions for package inserts and labels, in order to complement the contents of package inserts and packaging of the different classes of medicines sold in Brazil with a view to provide greater quality and safety to users and prescribers (ANVISA, 2003).

Understanding this information is an essential factor for the rational use of medicine (Cavaco, Santos, 2012). In this sense, this document must be formulated with a high-quality standard, with impartial and scientifically based information, even when it is available in the format for the patient (Pires, Vigário, Cavaco, 2015). Relevant information that should be included in package inserts refers to interactions between medicine and food (ANVISA, 2021). A medicine-food interaction is defined as an interaction resulting from a physical, chemical, physiological or pathophysiological relationship between a

medicine and a nutrient, multiple nutrients, food in general or nutritional status. An interaction is considered clinically significant when it alters the pharmacotherapeutic response or compromises the patient's nutritional status (Boullata, Armenti, 2010).

The simultaneous use of medicine and food can interfere with the kinetics and/or dynamics of the medicines, as well as with the digestion, absorption and use of nutrients (Anjos, *et al.*, 2019). The mechanisms that explain the effect of food and its consequences on medicine may involve several factors, including postprandial physiology, properties of the medicine, and how it is administered. In this sense, it is essential to have a complete understanding of these mechanisms when recommending whether a specific medicine should be administered with or without food (Deng, *et al.*, 2017).

For many years, interactions between medicine and food were little mentioned in the literature; this began to change with the publication of classic findings, such as the influence of vitamin C deficiency on the action of barbiturates, the influence of iron on the absorption of tetracycline, the influence of isoniazid on vitamin B6 metabolism, as well as on the impact of malnutrition on medicine bioavailability, the effect of food on medicine absorption, and the influence of medicines on nutrient absorption (Boullata, Armenti, 2010). Even in the face of current knowledge and the clinical relevance of medicine-food interactions, this subject is still little explored and has not been incorporated into the general knowledge of health professionals, scientists and regulatory agencies, which in turn have the capacity to

make significant contributions about the subject (Boullata, Armenti, 2010). In this sense, the package insert is an important tool for disseminating knowledge about these interactions. However, it is important that package inserts contain complete information so that they can serve as a vehicle for correct and safe information, not only for health professionals but also for the general population (Singhal, *et al.*, 2023). In addition, there is a gap in the literature regarding studies that compare what is available in scientific databases with the information provided on package inserts.

Considering the importance of this information for patients and health professionals, the present study aims to analyze the existence of information on medicine-food interactions in Brazilian package inserts and whether this information agrees with the literature.

## **MATERIAL AND METHODS**

This descriptive documentary study investigated the presence of information on medicine-food interactions in Brazilian package insert intended for patients and health professionals. The package inserts were obtained electronically from the database made available by the Brazilian Health Regulatory Agency (Agência Nacional de Vigilância Sanitária – ANVISA) (<http://consultas.anvisa.gov.br/#/bulario/>).

The selection of medicines was based on the 2022 edition of the National List of Essential Medicines (Relação Nacional de Medicamentos Essenciais – RENAME), which is published biennially and includes medicines and materials intended to meet the priority health needs of the Brazilian population (RENAME, 2022). RENAME is organized into five annexes:

Annex I – National List of Basic Component Medicines; Annex II – National List of Strategic Component Medicines; Annex III – National List of Specialized Component Medicines; Annex IV – National List of Materials; and Annex V – National List of Medicines for Hospital Use.

In this study, only medicines listed in Annex I were considered, as they are intended to address prevalent and priority conditions in Primary Health Care. This annex comprises 185 medicines. From this list, only orally administered medicines were selected. Subsequently, medicines with potential food interactions were identified using the *Handbook of Drug–Nutrient Interactions* (second edition, 2010) as the reference source (Boullata; Armenti, 2010). For medicines identified as having food interactions, the corresponding electronic package inserts intended for patients and for health professionals were retrieved from the ANVISA database using both the trade name and the active ingredient. When more than one package insert was available, the version with the most recent publication date was selected. Data collection was conducted from January 6 to February 28, 2021, and subsequently reviewed from December 1, 2021 to February 28, 2022.

Data were collected and organized using a Microsoft Office Excel® spreadsheet (version 2016), including the name of the active

ingredient, information on medicine–food interactions described in the reference handbook, and information presented in the package inserts intended for health professionals and patients. A comparative analysis was performed between the information contained in the handbook and that presented in the respective package inserts.

To classify the data as concordant, the information contained in the package inserts had to be similar to that described in the handbook. Partial agreement was defined when the information presented in the package inserts corresponded to one or more aspects described in the handbook, which contained more comprehensive information. Non-compliance was defined when the information in the package inserts differed from that presented in the handbook. Missing information was defined when information described in the handbook was absent from the package inserts. The categorization of the results is presented in Table I.

The data were analyzed descriptively using frequency distribution for categorical variables. The analysis was conducted independently by two researchers, and any disagreements regarding terminology or classification were discussed until a consensus was reached.

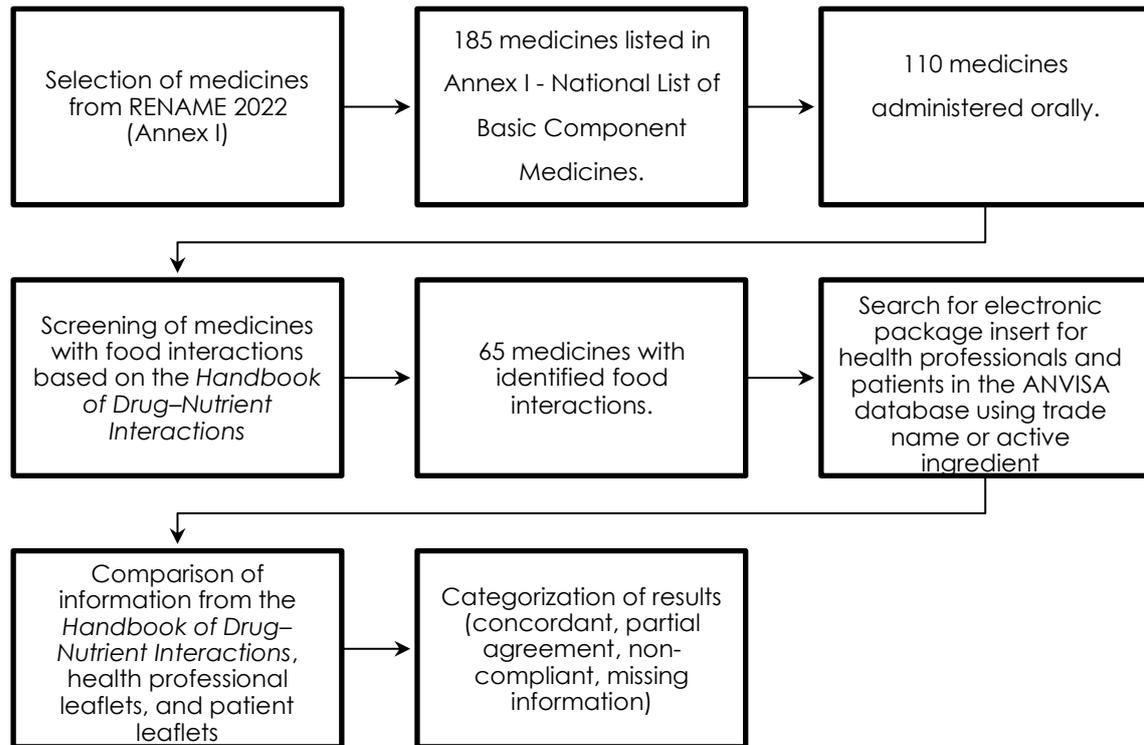
**Table I – Study variables and their category**

<b>Study variables</b>	<b>Classification / category</b>
<b>Information contained in the health professional package insert is in accordance with the reference source</b>	(1) yes (2) partial agreement (3) no (4) missing information
<b>continued table.</b>	
<b>Information contained in the patient package insert is in agreement with the reference source</b>	(1) yes (2) partial agreement (3) no (4) missing information
<b>Information contained in the health professional package insert is in accordance with the patient package insert</b>	(1) yes (2) partial agreement (3) no (4) missing information
<b>Type of Interaction</b>	(1) pharmacokinetic (2) pharmacodynamic (food/nutrient interferes with the action of the medicine) (3) medicine interferes with the patient's nutritional status (absorption/excretion)
<b>The interaction</b>	(1) reduces the effect of the medicine (2) increases the effect of the medicine (3) increases the excretion of nutrients (4) increases nutrient absorption
<b>If pharmacokinetic, type of interaction</b>	(1) absorption (2) distribution (3) metabolism (4) excretion
<b>Interaction with food</b>	(1) food in general (2) specific food
<b>If with specific food</b>	Which?

## RESULTS

A total of 110 orally administered medicines were selected from the RENAME list (Figure 1). When using the Handbook of Drug-Nutrient Interactions as a reference source, it was found that of the 110 medicines administered orally, 65 (59.1 %) had some interaction with food (Boullata, Armenti, 2010).

Figure 1. Research flowchart



RENAME National List of Essential Medicines; ANVISA National Health Surveillance Agency Source: (Boullata JI, Armenti VT, 2010).

Comparing the information in the Handbook with the health professional's package insert, it was observed that there was agreement in the information in 6 (9.2 %), partial agreement in 22 (33.8 %), no agreement in 22 (33.8 %) and non-existent data in 15 (23.1 %) in the health professionals' package inserts.

Comparing the information contained in the Handbook with the patient's package insert, it was found that in 6 (9.2 %) there was agreement on the information, partial agreement in 19 (29.2 %), no agreement in 17 (26.2 %) and lack of data in the patient's package inserts in 23 (35.4 %).

When comparing the information on medicine-food interactions in the health professional's package insert and in the patient's package insert, it was observed that there was agreement of information in 36 (55.4 %), partial agreement in 2 (3.1 %), non-agreement in 8 (12.3 %) and absence of data on medicine-food interactions in 19 (29.2 %) of the package insert consulted (Table II).

**Table II** – Agreement between consultation sources

Variable	N=	Yes	Partial agreement	No	Information missing
<b>Agreement between the Handbook and the professional package insert</b>	65	06 (9.2%)	22 (33.8%)	22 (33.8%)	15 (23.1%)
<b>Agreement between the Handbook and the patient package insert</b>	65	06 (9.2%)	19 (29.2%)	17 (26.2%)	23 (35.4%)
<b>Agreement between the professional package insert and the patient package insert</b>	65	36 (55.4%)	02 (3.1%)	08 (12.3%)	19 (29.2%)

It was noted that some clinically relevant information about medicine-food interactions is not included in the package insert, for example, the patient package insert does not state that the interaction between azithromycin and food reduces medicine absorption by 50 % (Boullata, Armenti, 2010). Another example that does not have information on the package insert is carbamazepine. This medicine can impair the absorption or increase the degradation of folic acid, lead to homocysteine and B vitamins deficiency, especially vitamin B12, and in the case of valproic acid, can lead to mineral depletion of zinc, selenium, copper and vitamins such as folic acid and niacin (Boullata, Armenti, 2010).

Even more classic information was absent, as in the case of carvedilol, which is best administered in the presence of food, because food reduces the risk of orthostatic hypotension (Boullata, Armenti, 2010). For diazepam, co-

administration with caffeine-containing beverages and food may result in a reduction in its sedative and anxiolytic effects, however this information is also not included in the patient's package insert (Boullata, Armenti, 2010).

When characterizing the type of interaction between medicine and food, based on information obtained from the Handbook (Boullata, Armenti, 2010), in the professional and patient package insert, it was observed that most interactions were pharmacokinetic 47 (72.3 %), and in 5 (7.7 %) pharmacodynamic; in addition, in 40 (61.5 %) the medicine interferes with the patient's nutritional status, either leading to greater absorption of some nutrient or causing its excretion. In 27 (41.5 %) cases, the interaction can increase the medicine effect and in 22 (33.8 %) it can reduce the medicine effect, however, this variation between loss or increase of the therapeutic effect will depend on the type of food that is being consumed concomitantly

with the medicine. In 34 (52.3 %) of the cases, the interactions could cause malabsorption or excretion of some nutrient in the diet and in nine (13.8 %), there could be an increase in the retention of some nutrient in the diet.

When the type of interaction was pharmacokinetic, in 36 (76.6 %) the interaction occurs during the process of medicine

absorption, in one (2.1 %) during medicine distribution and in 10 (21.3 %) during medicine metabolism. The most important interactions are caused by changes in medicine absorption due to the chemical reaction between the medicine and food, or the physiological response to food (Table III).

**Table III** - Characteristics of medicine-food interactions

Variable	Description	n = 65
<b>Type of Interaction</b>	Pharmacokinetic	47 (72.3%)
	Pharmacodynamic (food/nutrient interferes with medicine action)	5 (7.7%)
	Medicine interferes with the patient's nutritional status (absorption/excretion)	40 (61.5%)
<b>The interaction</b>	Reduces the effect of the medicine	22 (33.8%)
	Increases the effect of the medicine	27 (41.5%)
	Increases nutrient excretion	34 (52.3%)
	Increases nutrient absorption	09 (13.8%)
Variable	Description	n = 47
<b>If pharmacokinetic, type of interaction</b>	Absorption	36 (76.6%)
	Distribution	01 (2.1%)
	Metabolism	10 (21.3%)
	Excretion	0

Interactions between medicine and food can occur between foods in general (35.4 %) or specific foods (49.2 %). Among specific foods, grapefruit is the most mentioned food in these interactions and appears sixteen (24.6 %) times. This is because many medicines are metabolized with the help of the CYP3A4 enzyme, present in the intestinal epithelial tissue, and grapefruit juice can block the action of CYP3A4, so instead of

the medicine being metabolized, it remains in the bloodstream, which can lead to toxicity (Marin, Maluvayshi, Waitzberg, 2018). In addition to this food, caffeine appears eight times (12.3 %), which may reduce the sedative and anxiolytic effects of benzodiazepines and barbiturates (Boullata, Armenti, 2010). Milk and derivatives appear five times (7.7 %) and protein foods, fibers, and orange juice four (6.2 %) times. In addition to these, specific

foods such as tamarind, cranberry, foods rich in fat and foods containing phytates and oxalates were pointed out (Marin, Maluvayshi, Waitzberg, 2018).

## DISCUSSION

Of the medicines administered orally, 59.1 % had some interaction with food. Most package inserts for these medicines had missing or divergent information regarding medicine-food interactions. The results of the present study reveal gaps in information, both in the health professional's package insert and in the patient's package insert. Considering that package inserts are the main sources of information about medicines, both for health professionals and for patients (Santos, Feitosa, Dalcin, 2019), these discrepancies in information make the use of these sources for clinical guidance problematic. An adequate understanding of the prescribed treatment is necessary, either for a rational dispensation of the medicine, or for the fulfillment of an adequate therapeutic regime. It is expected that the treatment will not fail or that it will not predispose patients to adverse reactions that can be fatal. These aspects highlight the importance of familiarizing and sensitizing health professionals and patients to the existence of these interactions, with a view to optimizing therapeutic efficacy and minimizing medicine toxicity, since the interaction between medicine and food is a problem of great relevance in clinical practice, due to potential changes in the expected effects of the medicine (Marin, Maluvayshi, Waitzberg, 2018). It is essential that the health professional traces a careful profile

of the patient, including all of their physiological, nutritional and pharmacological aspects, considering the need for individual assessment in order to predict and prevent possible adverse reactions resulting from a possible medicine-food interaction.

It is worrying to note that a large number of these interactions are not mentioned in the health professional's package insert and in the patient's package insert. It is important to point out that when comparing the professional's package insert and the patient's package insert, it was found that about 12 % of the package inserts have divergent information between them. These disagreements should not exist, since the package inserts must contain the same instructions, but in different language styles, with the professional package insert containing more technical language and the patient package insert using simpler language so that every patient clearly understands the information about the medicine (ANVISA, 2021).

The identification of medicine-food interactions requires a multidisciplinary approach, involving pharmacists, nurses, nutritionists, and physicians, all of whom must be aware of these interactions in order to properly advise patients. Evidence from the literature indicates important knowledge gaps among these professionals and among the general population. In a cross-sectional study that assessed pharmacists' knowledge regarding medicine-food interactions using a validated questionnaire, the authors reported unsatisfactory levels of knowledge on this

topic (Zawiah et al., 2020). Similarly, a study evaluating nurses' knowledge, attitudes, and awareness found that 72.3% of nurses did not consider medicine–food interactions in their clinical practice (Enwerwm & Okunji, 2015). In addition, a recent study assessing the general public's level of knowledge and awareness demonstrated inadequate understanding of basic and fundamental aspects of medicine–food interactions, highlighting the urgent need to raise awareness among patients as well (Zaide et al., 2021).

Given this context, the availability of correct and adequate information about medicines is an important aspect to allow patients to better understand their medicines, resulting in greater adherence and reduced chances of negative effects related to medicine use. The short contact time between patients and health professionals makes the availability of written information an immediate and readily available means of obtaining all important information about the medicines in hand (Sillo *et al.*, 2018). In this sense, the package insert represents the main information material provided to patients when purchasing medicines produced by the pharmaceutical industry. However, gaps in important information for users reduce their value as an educational material.

A study, analyzed the existence of lack of information in package inserts on the correct handling of transdermal therapeutic patches and concluded that, although the package inserts analyzed were in accordance with the regulatory content requirements for approval, they did not comprehensively inform patients about

important aspects of the use of this type of medicine, showing a need to propose improvements in the package inserts in order to avoid failures in the therapeutic process (Lampert, Haefeli, Seidling, 2019). Furthermore, it is important to mention that different pharmaceutical companies generally use identical text on the package inserts, so, no matter what brand of medicine is used, the text will often be the same (ANVISA, 2021).

With regard to the type of interactions found, the present study focused on pharmacokinetic interactions because they are the most common and because they are considered clinically significant for altering the therapeutic response of the medicine or for compromising the nutritional status of the patient, resulting in some degree of malnutrition (Marin, Maluvayshi, Waitzberg, 2018).

Among the specific foods that interact with medicines, grapefruit appeared several times on the list and despite being a little known and used fruit among Brazilians, it must be remembered that many imported products are sold in Brazil (Marin, Maluvayshi, Waitzberg, 2018). It is not necessary to eat large amounts of this fruit for this association to be relevant. Drinking a glass of grapefruit juice, in combination with certain medicines, can lead to serious adverse effects such as gastrointestinal bleeding, kidney failure, breathing problems and even sudden death (Petric, *et al*, 2020; Chen *et al*, 2018). Caffeine, a substance present in some foods, also appeared more often on the list of interactions. It should be remembered that coffee, a much-appreciated drink that is part

of Brazilian cuisine, is a source of caffeine, however, there are other foods that have this substance, such as some types of soft drinks, chocolates, and teas such as green tea, mate tea, and black tea (Nehlig, 2018). Caffeine interacts with many medicines and may interfere with pharmacotherapeutic treatment, as it reduces therapeutic effects. Among these interactions we can mention: the increase in the absorption and bioavailability of paracetamol and acetylsalicylic acid, the decrease in theophylline clearance and competitive inhibition of clozapine metabolism, which may increase its plasmatic concentrations and the probability of the appearance of adverse effects (Tavares, Sakata, 2012).

Other specific foods such as milk and derivatives, protein foods, fiber, orange juice, foods containing phytates and oxalates, and cranberries appeared few times in the list of interactions; however, this does not mean that the fact that the food was mentioned not many times make it less harmful when interacting with a medicine. To exemplify, we can mention the simultaneous use of orange juice and the medicine alendronate sodium, this combination reduces the bioavailability of the medicine by approximately 60 % (Boullata, Armenti, 2010). Another example would be the interaction between anti-Parkinson medicines and a high-protein diet. The concomitant use of yeast/carbidopa and a high-protein diet can prevent medicine absorption, leading to loss of effectiveness and fluctuations in clinical manifestations (Boullata, Armenti, 2010; (Marin, Maluvayshi, Waitzberg, 2018).

In view of the above, we hope that the results of this research can be used by the regulatory agencies, analysis, and approval of Brazilian medicine package inserts, since an urgent need was identified to propose improvements in the content of the package inserts regarding interactions between medicines and food. To the best of our knowledge, this is the first study to assess the existence of information on medicine-food interactions in Brazilian medicine package inserts and whether there is agreement with the literature. There are no similar studies so that we can compare the results, so there is a gap in the literature on this subject. The results of this research highlight the importance of alerting health professionals and patients that often, the information provided in package inserts should not be used as the only source for guidance on medicine management. In this way, the present results can also be used by policy makers to design appropriate educational interventions to promote knowledge of medicine and food interactions among health professionals and patients. In addition, the results contribute to enrich the limited literature available on this subject.

Some limitations of our study must be addressed. When searching for information contained in the package inserts registered in the ANVISA electronic package insert list, we found that many medicines had several package inserts registered by different laboratories, therefore, we selected those with the most recent registration date, regardless of the manufacturer. With this approach, it may be that one or another package insert that we did not evaluate may have more information

about medicine-food interactions. In addition, we cite the Handbook itself as a limitation, since we used this single literary source to compare with the package inserts. However, we chose the Manual as our only source of literature because it is extremely well referenced. In addition, because it is complete and detailed, it covers practically all aspects of nutrition and pharmacology.

## CONCLUSION

Divergences and lack of information on interactions between medicine and food were found, both in the professional package insert and in the patient package insert. The absence of continued updating, the omission, or lack of completeness of relevant information, reduces its value as informative/educational material. These factors can lead to greater exposure to risks related to changes in medicine response and patient safety. Based on the problems encountered, it is believed that Brazilian medicine package inserts need to undergo improvements with regard to the information contained in these package inserts about medicine-food interactions and, thus, may become a most useful information/educational instrument. The results of this research highlight the importance of alerting health professionals and patients

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about the existence and relevance of these interactions and that, often, the information contained in package inserts should not be used as the only source for guidance on medicine management.

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## AUTHORS' CONTRIBUTIONS

**RCS; SIVG; SRS; PML; BAO and RDRA:** conception; data curation; formal data analysis; fundraising; research; methodology; project management; resources; supervision; validation; visualization; writing; original draft, writing, revision and editing.

## CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest of any kind.

## USE OF GENERATIVE ARTIFICIAL INTELLIGENCE

The authors declare that they have not used AI of any kind.

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