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Review article

Impact of drug-food interaction on the effectiveness of community disease treatment

Impacto da interação fármaco-alimento na eficácia do tratamento de doenças da comunidade

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ABSTRACT

Drug interactions occur when the effects of a drug are altered by another drug or food, and may be physicochemical, pharmacokinetic or pharmacodynamic. Drug-food interactions involve cytochrome P450 enzymes and P-glycoprotein, impacting the efficacy and safety of the treatment of diseases in the community. Foods such as grapefruit, dairy products and alcohol can modify the effects of antihypertensives, antidepressants, NSAIDs and anticoagulants, among others. Drug-drug interactions (DDIs) account for 26% of adverse events, increasing hospitalizations. Of the 1658 articles found in PubMed, 40 were selected, highlighting that food can interfere with the efficacy and safety of antihypertensives, antidepressants, NSAIDs and anticoagulants, increasing the risk of toxicity and decreasing absorption, demonstrating the importance of considering diet when prescribing medications to optimize treatment efficacy and minimize risks. Training healthcare professionals is crucial to ensuring safe and effective treatment in the community.

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RESUMO

As interações medicamentosas ocorrem quando os efeitos de um medicamento são alterados por outro fármaco ou alimento, podendo ser físico-químicas, farmacocinéticas ou farmacodinâmicas. Interações fármaco-alimento envolvem enzimas do citocromo P450 e glicoproteína P, impactando a eficácia e segurança do tratamento de doenças da comunidade. Alimentos como toranja, laticínios e álcool podem modificar os efeitos de anti-hipertensivos, antidepressivos, AINEs e anticoagulantes, entre outros. As interações entre medicamentos (drug-drug interactions - DDIs) representam 26% dos eventos adversos, aumentando hospitalizações. Dos 1658 artigos encontrados no PubMed, 40 foram selecionados, destacando que alimentos podem interferir na eficácia e segurança de anti-hipertensivos, antidepressivos, AINEs e anticoagulantes, aumentando riscos de toxicidade e diminuindo absorção, demonstrando a importância de considerar a dieta ao prescrever medicamentos para otimizar a eficácia do tratamento e minimizar riscos. A capacitação dos profissionais de saúde é crucial para garantir um tratamento seguro e eficaz na comunidade.

INTRODUCTION

Drug interactions occur when the effects of a medication are altered by the presence of another drug, food, beverage, or environmental chemical agent[1]. These interactions can be classified as physicochemical, pharmacokinetic, or pharmacodynamic. Pharmacokinetic interactions involve the processes of drug release, absorption, distribution, metabolism, and/or excretion, impacting its therapeutic efficacy and safety. Pharmacodynamics concerns the drug's mechanism of action, which may reduce or amplify its therapeutic effect[2].

Pharmacokinetic interactions involve cytochrome P450 enzymes and P-glycoproteins. This P-glycoprotein acts as an efflux pump for drugs that are its substrates, affecting their bioavailability and absorption[2]. Pharmacodynamic interactions occur when foods or other medications modify the clinical effect of a drug in the body, causing additive, synergistic, or antagonistic effects. Foods such as fruits (especially grapefruit), dairy products, vitamin K, tyramine-containing foods, and alcohol can interact with medications, altering their efficacy and safety[3].

Drug-drug interactions occur when one drug enhances or diminishes the effect of another and are responsible for 26% of all adverse drug events, being associated with increased hospitalization rates[1]. Among the most common are those resulting from additive effects, such as the combination of drugs that increase the risk of seizures, prolong the QT interval, intensify central nervous system depression, and raise the likelihood of serotonin syndrome.

In this context, patient counseling and collaboration among healthcare teams are essential to prevent undesirable interactions. Clinical decision support related to medications has proven effective in improving patient care quality and reducing the rate of adverse events. However, alerts generated by these systems must be interpreted with clinical judgment, taking into account the risks and benefits of the medications within the individual context of each patient. In this regard, family physicians play a crucial role in identifying and preventing clinically significant interactions, optimizing treatment safety through the use of drug interaction software and collaboration with pharmacists, thereby ensuring greater patient safety[4].

Among the types of drug interactions, the interaction between drugs and food has a major impact on the treatment of diseases within the community, causing various clinical consequences by altering the absorption, distribution, metabolism, and excretion of drugs in the body. In addition, the socioeconomic effect of these interactions includes increased healthcare costs due to preventable hospitalizations and a decline in patients' quality of life. The lack of information among the population, the insufficient qualification of healthcare professionals, and the limited discussion of this topic are factors that exacerbate the situation, compromising the efficacy and safety of medications and the treatment of common diseases affecting the population, such as diabetes and hypertension[1].

Foods interact with drugs at the molecular level through their natural composition. These compounds are biologically active and therefore interact with medications[2]. Foods primarily impact the pharmacokinetics of drugs by influencing absorption. They can delay gastric emptying, alter gastrointestinal pH, increase hepatic blood flow, and affect liver metabolism. Each food has a distinct nutritional and caloric composition, with varying amounts of proteins, fats, and carbohydrates, leading to different effects on drug dissolution and permeability. Thus, certain foods have a significant impact on the systemic availability of drugs essential for managing chronic diseases[5].

From this perspective, it is extremely important to understand potential interactions in order to educate patients about appropriate

dietary habits and what to avoid, in addition to preventing adverse effects and ensuring maximum effectiveness. In this context, it is crucial that physicians are guided on strategies for managing and minimizing the risks of interactions in clinical practice. This is because increasing the drug dose is not always the best approach to improving effectiveness; rather, correcting the food-drug interaction may be more appropriate. This paper will address drug-food interactions in specific populations, such as hypertensive individuals, patients with depression, and those using NSAIDs and anticoagulants.

MATERIALS AND METHODS

This review was a study conducted through a bibliographic survey of scientific material obtained from the PubMedline database. The initial search term was "drug-nutrient interaction," which resulted in a total of 4,266 articles. Another search term used was "food-drug interaction," yielding a total of 1,658 results. Subsequently, more specific searches were conducted regarding the conditions addressed, such as "Interactions between antihypertensive drugs and food," "Interactions between antidepressants and food," "Interactions between NSAIDs and food," and "Interactions between anticoagulants and food." The selection of articles followed a rigorous process. Initially, titles and abstracts were reviewed. In the following stage, the remaining studies underwent critical evaluation, considering their relevance to the topic, clarity of information, and clinical significance. Duplicates, articles without abstracts, those not directly related to the review objective, and those published more than 15 years ago were excluded. At the end of the process, 40 articles were selected to form the basis of this study.

RESULTS AND DISCUSSION

Of the 40 articles selected for analysis, the main findings are presented in **tables 1 to 4**.

Table 1. Drug Interactions Between Food and Antihypertensive Medications

AUTHORS	RESULTS
Choi&Ko, 2017; Mason, 2010[6,7]	The bioavailability and efficacy of antihypertensive drugs are influenced by the cytochrome P450 enzyme system, especially the CYP3A4 enzyme, which metabolizes approximately 50% of these medications. Foods that inhibit CYP3A4 increase drug bioavailability, raising the risk of toxicity.
Nicoletti et al., 2023[8]	The administration of doxazosin with high-fat foods increases the concentration of the drug in the bloodstream, whereas beta-blockers such as metoprolol and timolol are not significantly affected by food intake. The bioavailability of propranolol is increased when taken with high-protein diets and in combination with garlic.
Choi&Ko, 2017[6]	Diuretics such as furosemide and bumetanide have reduced bioavailability when administered with food, whereas spironolactone and hydrochlorothiazide have increased absorption.
Nicoletti et al., 2023; Jáuregui-Garrido& Jáuregui-Lobera, 2012[8,9]	Grapefruit juice inhibits CYP3A4 and increases the bioavailability of several calcium channel blockers—except amlodipine—potentially leading to toxicity.

Table 2. Drug Interactions Between Food and NSAIDs.

AUTHORS	RESULTS
Mattiello et al., 2011; Kim et al., 2022[10,11]	The intake of coffee and caffeine suppresses the expression of Mrp4, an efflux transporter of aspirin and salicylic acid, without affecting P-gp and BCRP.

Table 2. Continuation.

Kim et al., 2022; Kim D.H., 2018[11,12]	The gut microbiota metabolizes aspirin into salicylic acid and other compounds, affecting its reabsorption and efficacy.
Kim et al., 2022[11]	Gastric acidity favors the absorption of aspirin by maintaining it in its non-ionized form.

Table 3. Drug Interactions Between Food and Antidepressants

AUTHORS	RESULTS
Siwek et al., 2023[13]	The liquid used to ingest antidepressants can affect their efficacy, with very hot water causing premature dissolution of the enteric coating. Tannins and polyphenols present in coffee or tea reduce the absorption of antidepressants. Cytochrome P450 inhibitors such as grapefruit juice, citrus fruits, cranberry juice, tomatoes, garlic, and peppers increase the concentration of antidepressants in the body, enhancing their effects.
Gezmen-Karadağ et al., 2018; Mrozek et al., 2023[14,15]	Dietary fiber and high-fat meals can adsorb or increase the absorption of antidepressants, respectively, altering their blood concentration and intensifying side effects.
Siwek et al, 2023[13]	Foods such as vegetables from the Brassicaceae family, grilled meat, soy, ginger, and spices like black pepper, cinnamon, cloves, and nutmeg are cytochrome P450 inducers, reducing the efficacy of antidepressants.
Mrozek et al., 2023[15]	Supplements such as St. John's Wort should not be used with SSRIs and TCAs due to the increased risk of side effects. *Ginkgo biloba,* Kava-kava, Ginseng, and Valeriana officinalis may intensify the effects of antidepressants.
Gezmen-Karadağ et al., 2018[14]	MAOIs interact with tyramine-rich foods, such as aged cheeses and smoked meats, potentially causing hypertensive crises.

Table 4. Drug Interactions Between Food and Anticoagulants.

AUTHORS	RESULTS
Yang et al., 2017[16]	It was found that cranberry juice (CJ) decreased the bioavailability of both forms of warfarin when consumed prior to drug administration, but inhibited the elimination of S-warfarin when consumed 10 hours after warfarin.
Di Minno et al., 2017[17]	It was stated that warfarin has a narrow therapeutic range, which requires constant INR monitoring and frequent dosage adjustments. • **Grapefruit:** Inhibits CYP3A4, potentially increasing INR and causing bruising. • **Green tea:** Can significantly reduce INR at high doses, but moderate consumption is considered safe due to its low vitamin K content. • **Chamomile:** Inhibits CYP1A2, CYP3A4, and CYP2C9 in vitro, with one reported case of hemorrhage in a patient consuming large quantities while on warfarin therapy. • **Soy:** Inhibits CYP3A4 and CYP2C9 in vitro, and may reduce the anticoagulant activity of warfarin due to its vitamin K content. • **Mango:** Contains retinol, a CYP2C19 inhibitor, which may clinically increase INR. • **Ginseng:** Does not alter the metabolism or efficacy of warfarin. • **St. John's Wort:** Induces CYP1A2, CYP2C9, and CYP3A4, increasing warfarin clearance and reducing its efficacy. • ***Ginkgo biloba*:** May increase the risk of bleeding; certain flavonoids in Ginkgosp inhibit CYP2C9.
Güllü&Dede., 2016[18]	Thymoquinone: Significantly inhibits the CYP2C9-catalyzed hydroxylation of tolbutamide, suggesting that it may interfere with the metabolism of drugs processed by this enzyme.

Antihypertensives

Hypertension is a disease that can be managed through lifestyle measures such as stress control, reducing excessive salt intake, and engaging in physical activity. However, alongside these measures, pharmacological treatment with antihypertensive drugs—such as diuretics, alpha- and beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, and angiotensin II inhibitors, among others—is required[8].

The bioavailability and efficacy of these drugs depend on their metabolism by the cytochrome P450 enzymatic system in the liver and gastrointestinal tract, with the main isoform being the CYP3A4 enzyme, responsible for metabolizing about 50% of these medications. The lower the enzymatic activity and metabolism, the higher the drug's bioavailability, which increases the risk of side effects and toxicity—especially for drugs with a narrow therapeutic window[6]. Some foods inhibit CYP3A4 and alter drug metabolism, increasing bioavailability. Therefore, if a patient consumes a food that also requires CYP for its own metabolism, this can lead to drug toxicity.

Additionally, P-glycoprotein located at the brush border of enterocyte membranes is a membrane transporter that acts on antihypertensive drugs. Certain foods inhibit P-glycoprotein (an efflux pump into the intestinal lumen). Inhibition of this transporter increases the absorption of antihypertensives[7].

The oral administration of loop diuretics, such as furosemide and bumetanide, along with food reduces the bioavailability of these drugs. However, in patients with protein-calorie malnutrition, the bioavailability of orally administered furosemide increases due to a reduction in hepatic first-pass metabolism. In the case of spironolactone, this drug interacts with food by increasing its absorption and reducing first-pass metabolism[8]. This increase in bioavailability also occurs with hydrochlorothiazide. Indapamide, however, is not affected by food intake[9].

The mechanism of action of α1-adrenergic and β-adrenergic receptor blockers is to competitively and reversibly block these receptors, reducing the action of catecholamines, which are unable to act on them. Additionally, some of these drugs release nitric oxide or block α-adrenergic receptors, resulting in vasodilation[9].

The administration of doxazosin with high-fat meals leads to a higher maximum concentration compared to fasting conditions. Beta-blockers such as metoprolol and timolol are not significantly affected by simultaneous food intake. The bioavailability of propranolol increases when taken with a high-protein diet, while high-carbohydrate, low-protein diets do not alter the drug's bioavailability. Another food-drug interaction involving propranolol is with garlic, a plant that contains sulfur compounds which act similarly to beta-blockers, enhancing their effect without causing serious clinical consequences[8].

Additionally, beta-blockers such as propranolol are metabolized by CYP2D6, which is affected by garlic. Antihypertensive drugs such as angiotensin-converting enzyme (IACE) inhibitors and calcium channel blockers also have their hypotensive effects enhanced[7].

Ginger contains substances with vasodilatory properties, such as terpineol, which can cause hypotension. When combined with an antihypertensive drug, ginger may potentiate the antihypertensive effect[8].

Grapefruit juice is rich in vitamins and has a strong antioxidant effect; however, it can cause a high rate of interactions and toxicity with antihypertensive and antiarrhythmic drugs[8]. Grapefruit juice affects drug metabolism by inhibiting cytochrome P450 enzymes (CYP3A4), increasing the bioavailability of drugs, and its effects can last up to 24 hours after ingestion. Amlodipine does not interact with grapefruit juice[9].

Orange and apple juice greatly reduce the

bioavailability of atenolol, decreasing its antihypertensive efficacy. Apple juice contains flavonoids that interfere with intestinal absorption of atenolol through the sensitivity of the plasma membrane monoamine transporter (PMAT/SLC29A4) to this substance. Therefore, dose adjustment is necessary when administering atenolol with orange or apple juice, or the juice should be consumed separately from the drug. Orange juice also significantly decreases celiprolol concentrations. The ingestion of orange juice, which has an acidic pH (3.5), lowers the pH of the intestinal lumen, reducing the amount of non-ionized drug—the absorbable form of this basic, hydrophilic medication[19]. Green tea inhibits the organic anion transporter (OATP1A2), reducing the plasma concentration of the beta-blocker nadolol[2].

Felodipine is one of the calcium channel blockers with a high potential for interaction with grapefruit juice and bitter orange juice (Seville orange). To avoid this, the patient may consume grapefruit juice at least 2 to 3 days prior to the administration of the medication. However, the best recommendation to prevent such interactions is to eliminate grapefruit juice from the diet of patients with cardiovascular disorders[9].

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medications in the world and are included in the WHO Model List of Essential Medicines due to their great importance[20]. NSAIDs assist in the treatment of conditions such as osteoarthritis, rheumatoid arthritis, acute gout, and headaches. These drugs have anti-inflammatory, analgesic, and antipyretic effects. Their mechanism of action involves the inhibition of the cyclooxygenase (COX) pathway, which produces prostaglandins and other substances that intensify the inflammatory process[21].

Commonly used drugs include acetylsalicylic acid (aspirin), dipyrone, diclofenac, and ibuprofen. Improper and prolonged use of NSAIDs can increase the risk of gastrointestinal, cardiovascular, hepatic, cerebral, and renal side effects[20]. Therefore, careful attention must be given to the duration and dosage of NSAID use to ensure the rational use of these medications[21].

The efficacy of these drugs is determined by the plasma concentration they are able to achieve. It is common for patients to be advised to take NSAIDs with food in order to reduce gastrointestinal side effects. However, it is important to consider potential food-drug interactions that may reduce plasma bioavailability or delay the absorption of these anti-inflammatory drugs, thereby diminishing their pharmacological effects in the treatment of pain and inflammation[22].

Therefore, such interactions must be avoided to ensure earlier and more lasting pain relief, reducing the need to re-administer the drug at higher doses and avoiding the replacement of these NSAIDs with more potent medications that may cause additional adverse effects and health risks, including renal and hepatic impairment.

Aspirin, also known as acetylsalicylic acid, is widely used for the treatment of pain, rheumatic fever, and inflammation. Once ingested, it is rapidly absorbed through the gastrointestinal tract and circulates in the bloodstream predominantly as salicylic and acetylsalicylic acid. During and after absorption, acetylsalicylic acid is converted into salicylic acid. A lower gastric pH favors this absorption by maintaining the drug in its non-ionized form. The resulting salicylic acid is responsible for the relief of pain, fever, and inflammation.

In the liver, salicylic acid is metabolized by conjugation enzymes such as UDP-glucuronosyltransferase and is then excreted mainly in the urine (over 80%) and, to a lesser extent, in bile (less than 5%). Salicylate conjugates secreted into the intestine via bile can be metabolized

back into salicylates by the gut microbiota and reabsorbed into the bloodstream. Gastrointestinal environmental factors, such as intestinal pH and the microbiota—which breaks down aspirin into ionized forms—can influence the reabsorption of salicylate conjugates. The administration of ampicillin in rats increases aspirin absorption into the bloodstream and enhances its analgesic effect[11].

Most orally administered medications are absorbed directly from the intestine into the bloodstream and are generally resistant to the gastric and biliary environments, as well as to the intestinal microbiota[23].

However, some drugs may be transformed into active, inactive, or toxic metabolites by digestive enzymes and the intestinal microbiota. The microbiota can metabolize hydrophilic drugs and phytochemicals—such as sulfasalazine and ginsenoside Rb1—into hydrophobic compounds, such as 5-acetylsalicylic acid and compound K. The human intestinal microbiota, present in both the small and large intestines, transforms unabsorbed food components and drugs in the gastrointestinal tract[12].

Alterations in the composition of the intestinal microbiota—affected by medications and diets—can influence drug absorption into the bloodstream in both humans and animals. Orally administered aspirin can be transformed into salicylic acid and 5-hydroxysalicylic acid by fecal microbiota and hepatic enzymes in humans and rodents. Thus, when aspirin is administered orally in rodents and humans, both aspirin and salicylic acid can be detected in the blood. If aspirin is metabolized into salicylic acid in the intestine, this metabolite is not easily absorbed into the bloodstream. However, pretreatment with ampicillin in mice increases the absorption of both aspirin and salicylic acid. This suggests that the hydrolysis activity of aspirin by the intestinal microbiota may be inhibited by ampicillin. Additionally, the co-administration of aspirin with caffeine significantly increases its absorption into the blood, due to increased gastric acid secretion induced by caffeine. Coffee consumption may modify the intestinal microbiota and its metabolites *in vivo*, though the effects on microbiota-mediated aspirin pharmacokinetics remain unclear[11].

In the study in question, it was observed that pretreatment with coffee for five days increased the area under the curve (AUC) of aspirin and salicylic acid in mice treated orally with aspirin. Oral administration of coffee significantly altered the composition of the intestinal microbiota in mice: it increased alpha diversity and changed beta diversity (Principal Coordinates Analysis, PCoA). Moreover, coffee treatment reduced the hydrolysis activity of aspirin by the intestinal microbiota. The combined treatment of aspirin with caffeine significantly increased the AUC of salicylic acid in humans compared to those who received aspirin alone. These results suggest that coffee intake may increase the absorption of salicylic acid and aspirin—rapidly hydrolyzed into salicylic acid during and after absorption—by inhibiting aspirin hydrolysis activity by the intestinal microbiota[12].

The combined treatment of aspirin with caffeine significantly increased the AUC of salicylic acid in humans compared to those who received aspirin alone. It was suggested that caffeine intake may enhance the absorption of orally administered aspirin in humans due to increased gastric acid secretion. Oral administration of aspirin with caffeine significantly improved analgesic activity in patients with sore throat and postoperative pain following oral surgery compared to those treated with aspirin alone. However, pretreatment with coffee or caffeine suppressed the expression of *Mrp4*, an efflux transporter of aspirin and salicylic acid, while the expression of *P-gp* and *BCRP* was not affected. The fecal microbiota of coffee-treated mice suppressed *Mrp4* expression in Caco-2 cells compared to those treated with vehicle[10].

Treatment with coffee extract or caffeine did not directly affect *Mrp4* expression in Caco-2 cells. These results suggest that the intake of

coffee and its component caffeine may increase aspirin absorption by inhibiting the expression of *Mrp4*, an efflux transporter[11].

Additionally, it has been reported that the intestinal microbiota hydrolyzes aspirin into salicylic acid, and suppression of its hydrolytic activity through antibiotic treatment increases the absorption of aspirin and salicylic acid into the bloodstream of rodents[24].

Caffeine treatment suppressed the absorption of aspirin and salicylic acid into the blood. These results suggest that coffee intake may enhance the absorption of salicylic acid and aspirin by inhibiting both the hydrolytic activity of intestinal microbiota and the expression of *Mrp4*. Moreover, coffee intake may increase the absorption of *Mrp4*-dependent drugs into the bloodstream. Further research is needed on the effect of coffee intake on microbiota-mediated pharmacokinetics of *Mrp4*-dependent drugs, and on the differences in microbiota-mediated aspirin metabolism between males and females, and between humans treated with or without antibiotics, including treatments involving both antibiotics and aspirin[11].

Antidepressants

Depression is one of the most common mental health conditions worldwide[25]. In recent years, there has been a notable increase in the incidence of this illness, particularly related to the COVID-19 pandemic[26]. This condition is associated with hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, dysregulation of neurotransmitter levels, reduced neurotrophic factors, and an imbalance in the immune system. Its pathophysiology is based on a deficiency of neurotransmitters such as serotonin, dopamine, and norepinephrine, along with a significant increase in pro-inflammatory cytokines that heighten metabolic stress, including interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor alpha (TNF-α). The medications used in treatment include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs)[27].

Antidepressants such as SSRIs can reduce depressive symptoms but may also cause undesirable effects by increasing serotonin (5-HT) activity while reducing norepinephrine and dopamine activity[28]. These adverse effects can decrease treatment adherence and delay patient recovery and return to normal daily activities. Some studies have shown that patients undergoing antidepressant therapy experienced a 5% weight gain, a significant side effect that can trigger various comorbidities and reduce life expectancy[29]. Furthermore, the delayed onset of medication action is another factor that hinders adherence to treatment[27].

This condition has a major impact on patients' quality of life and social participation. If left untreated, it can be fatal and is one of the leading causes of suicide attempts. Individuals with major depressive disorder (MDD) are prone to recurrent episodes of depression throughout their lives[30]. If remission does not occur for at least two months within a two-year period, the condition is classified as persistent depressive disorder or dysthymia. On the other hand, when a patient exhibits mild depressive symptoms, this is referred to as subclinical depression. In such cases, it is crucial to prevent the progression to major depression[15].

A proper diet and healthy lifestyle habits play an essential role in the prevention of depression and can serve as a valuable complement to psychological and pharmacological treatment. For example, vitamin D supplementation has proven highly effective in reducing depressive symptoms and preventing depression, especially in women. In the central nervous system, there are nuclear receptor complexes for vitamin D (VDRs) that exert genomic effects in the brain. Its action involves the synthesis of neurotransmitters such as serotonin, dopamine, adrenaline, and noradrenaline, the regulation of neurotrophins such as nerve growth factor (im-

portant for neuronal differentiation), and the control of inflammation through the reduction of pro-inflammatory cytokines, offering neuroprotection. Modulation of the serotonergic system by vitamin D has an antidepressant effect. Vitamin D deficiency causes structural and functional changes in the hippocampus—an essential region for the pathophysiological mechanisms of depression and where numerous VDRs are distributed[31].

Conversely, inadequate nutrition can decrease the efficacy of antidepressants or increase their side effects, resulting in potentially dangerous symptoms[15].

Antidepressants can be negatively affected by the liquid used for ingestion—very hot water can cause premature dissolution of the tablet or capsule's enteric coating. It is recommended to take antidepressants with warm, boiled water[13]. Tannins and polyphenols found in coffee or tea can reduce the absorption and efficacy of these medications. Food-drug interactions may occur during gastrointestinal absorption. Antacids, flax seeds (*Linum usitatissimum*), and plantago (*Plantago psyllium and Plantago ovata*) may reduce the effectiveness of antidepressants, particularly tricyclic antidepressants (TCAs) such as amitriptyline and doxepin. Dietary fibers such as bran, oats, legumes, barley, and buckwheat can adsorb tricyclic antidepressants, reducing their efficacy. To avoid this, a 1–2 hour interval between the ingestion of these foods and the administration of antidepressants is recommended[15].

The absorption of lipophilic antidepressants is affected by high-fat meals—such as fried eggs, bacon, butter, whole milk, and lard—which increase the absorption of these medications in the gastrointestinal tract[14]. This can raise the concentration of the drug and its metabolites in the blood, intensifying side effects such as altered consciousness, sleep disturbances, nervous system disorders, tachycardia, hypotension, seizures, agitation, and mydriasis[15].

Antidepressants are metabolized in the liver, affecting the activity of cytochrome P450 isoenzymes. During hepatic metabolism, many interactions occur between different drugs taken simultaneously[31]. Taking antidepressants alongside cytochrome P450 inducers increases their metabolism and reduces therapeutic efficacy. Antidepressants such as TCAs, fluoxetine, paroxetine, and fluvoxamine exhibit inhibitory effects on CYP450 isoenzymes, increasing the risk of drug interactions[15].

Nutrients and stimulants may act as inhibitors or inducers of cytochrome P450 isoenzymes. Inducers include vegetables from the Brassicaceae family, grilled meat, soy, ginger, and spices such as black pepper, cinnamon, cloves, and nutmeg. The active compounds in these foods affect various isoenzymes, intensifying drug degradation and reducing therapeutic effects—except in the case of prodrugs that require cytochrome P450 enzymes (especially CYP3A4 and CYP2D6) for conversion into their active forms[14].

Tobacco smoke is a significant inducer of cytochrome P450 isoenzymes and reduces treatment efficacy in smoking patients. Many P450 enzyme inhibitors interact with antidepressants, including grapefruit juice, citrus fruits and their juices, cranberry juice, legumes, tomatoes, parsley, thyme, garlic, licorice root, natural honey, peppers, chili, turmeric, black and long pepper. These inhibitors reduce antidepressant metabolism, potentially intensifying therapeutic or adverse effects. Antidepressant treatment requires restricting or abstaining from these foods and maintaining a proper time interval between medication intake and meals containing cytochrome P450 inhibitors or inducers[15].

Particular care should be taken with the consumption of grapefruit juice, citrus fruits, and chili peppers, as they contain bergamottin, naringin, narirutin (*in citrus*), and capsaicin (*in chili*), which strongly inhibit cytochrome P450 activity and increase drug concentrations in the body. Grapefruit juice

should be consumed at least 4 hours before or after taking the medication[13].

The use of herbal supplements and vitamin supplementation in the treatment of depression is also a relevant concern. St. John's Wort extract (*Hypericum perforatum*) is one such supplement used for mild to moderate depression by inhibiting the reuptake of neurotransmitters such as serotonin, dopamine, and norepinephrine[15]. St. John's Wort should not be used with selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). Supplements containing *Ginkgo biloba*, Kava-kava (*Piper methysticum*), Ginseng (*Panax ginseng*), and *Valeriana officinalis* can enhance the effect of antidepressants, increasing the risk of side effects. *Ginkgo biloba* may exacerbate side effects of phenelzine and trazodone to the point of inducing coma in some cases. Kava-kava intensifies the effects of fluoxetine, amitriptyline, clomipramine, and sedatives[15]. In addition to fluoxetine and amitriptyline, *Valeriana officinalis* also inhibits the metabolism of duloxetine, increasing the risk of adverse effects such as nausea, constipation, weight gain, and elevated heart rate[32].

MAOIs (such as moclobemide) block monoamine oxidase activity, inhibiting the metabolism of tyramine found in foods[14]. During therapy with these medications, tyramine-containing products must be eliminated from the diet. These include salami, pepperoni, cheeses (cheddar, Emmentaler, Camembert, Brie, blue cheese, mozzarella, Parmesan, Roquefort, Stilton, Gruyère), fish (marinated or smoked), beef liver (stored), chicken liver (stored), soy sauce, caviar, Bolognese sausage, meat concentrates (in sauces and soups), avocado, ripe bananas, chocolate, figs (canned or ripe), broad beans, yeast supplements, yeast extract, caffeine (in large amounts), vermouth, Chianti wine, and Chartreuse liqueurs. The interaction of MAOIs with tyramine-rich foods may lead to psychomotor agitation, vasoconstrictive tachycardia, and hypertension, posing a serious threat to life and health and, in some cases, resulting in a hypertensive crisis[15].

Anticoagulants

A Warfarin, a vitamin K antagonist, is widely prescribed as an oral anticoagulant for the prevention and treatment of thromboembolic disorders and recurrent transient ischemic attacks, as well as to reduce the risk of recurrent myocardial infarction. As an acidic substance (pKa = 4.94), warfarin exists in the body as an anion. Recently, it has been demonstrated that both S- and R-warfarin are transported by the breast cancer resistance protein (BCRP)[16], an ATP-binding cassette (ABC) class transporter with a broad range of substrates. In clinical practice, warfarin is administered as a racemic mixture (1:1), in which S-warfarin is 2 to 5 times more potent in terms of anticoagulant effect than R-warfarin. Pharmacokinetically, S-warfarin is primarily metabolized by cytochrome P450 (CYP) 2C9, while R-warfarin is metabolized by CYP1A2 and CYP3A4[17].

Warfarin has a narrow therapeutic range, making the determination of the optimal dose a challenge in clinical practice. Patients beginning treatment often experience adverse events such as bleeding, requiring constant monitoring of the International Normalized Ratio (INR) and frequent dosage adjustments. Several factors can influence the appropriate dosage, including the patient's diet, liver function, comorbidities, and the concomitant use of other medications[17]. Moreover, INR levels may be impacted by unpredictable individual responses and a wide variety of foods and drugs known to interact with warfarin[33].

Components of grapefruit, such as furanocoumarins, inhibit CYP3A4 activity. Although few cases of elevated INR and bruising have been reported, patients and physicians should be aware of this potential interaction with warfarin. Green tea, despite its health benefits, can significantly reduce INR at high doses, as re-

ported in cases where INR dropped from 3.8 to 1.4, indicating a possible significant interaction between green tea and vitamin K antagonists (VKAs). However, moderate green tea consumption is unlikely to affect anticoagulant therapy, as it contains little vitamin K, and the amounts of other compounds such as catechins and flavonoids are generally insufficient to significantly alter INR[17].

Furthermore, chamomile, commonly used as an herbal remedy for gastric discomfort and anxiety, inhibits CYP1A2 *in vitro* and, to a lesser extent, CYP3A4 and CYP2C9. To illustrate this scenario, a severe case of hemorrhage was reported in a 70-year-old patient undergoing warfarin therapy who was consuming large amounts of chamomile. Soy, used to manage menopausal symptoms and hypercholesterolemia, inhibits CYP3A4 and CYP2C9 *in vitro*, potentially reducing warfarin's anticoagulant activity due to its significant vitamin K content. Mango consumption, which provides high concentrations of retinol—a known CYP2C19 inhibitor—may clinically increase INR, even in small amounts, making it necessary to alert both patients and physicians to this interaction. Ginseng does not affect the pharmacokinetics or pharmacodynamics of warfarin[17].

St. John's Wort, used to treat mild depression, sleep disorders, and anxiety, induces CYP1A2, 2C9, and 3A4, increasing warfarin clearance and reducing its plasma concentrations. Prolonged use of this herb enhances the clearance of both the S-form (+29%, via CYP2C9) and R-form (+23%, via CYP3A4/CYP1A2) of warfarin, resulting in a significant reduction in warfarin's pharmacological effect. *Ginkgo biloba* may increase the risk of bleeding in surgical patients. Although one study found no difference in warfarin anticoagulation when taken concurrently with *Ginkgo spp.*, *in vitro* studies have shown that several flavonoids present in *Ginkgo biloba* are potent inhibitors of CYP2C9[17].

It has been reported that thymoquinone may present a potential risk for drug interactions by influencing drug-metabolizing enzyme activity. For example, it is believed that thymoquinone can increase plasma levels of glibenclamide by reducing the activity of CYP3A2 and CYP2C11 enzymes in rats[34].

Additionally, another study demonstrated that thymoquinone can significantly inhibit the hydroxylation of tolbutamide catalyzed by CYP2C9[18]. More recent studies have indicated that thymoquinone may also reduce phenytoin hydroxylation mediated by CYP2C9[35]. However, the inhibitory effects on CYP2C9 appear to vary depending on the substrate, possibly due to the presence of multiple binding regions within the CYP2C9 active site[36]. The authors then conducted a simultaneous determination of S- and R-warfarin in plasma using an LC/MS method[16]. The divergent profiles observed between S- and R-warfarin indicate stereoselective pharmacokinetics, in agreement with previous studies[37]. The S-warfarin form, which is the most pharmacologically active, showed higher plasma levels than R-warfarin, suggesting that S-warfarin was either more extensively absorbed, less metabolized, or more slowly excreted than R-warfarin.

Furthermore, the results of the pharmacokinetic study showed that cranberry juice (CJ) intake prior to warfarin administration decreased the Cmax and AUC_0–t of both S- and R-warfarin, indicating that CJ reduced the bioavailability of both forms of warfarin—consistent with the decreased warfarin efficacy reported in some clinical studies. Specifically, the AUC_0–t of S-warfarin was reduced by 34%, while that of R-warfarin was reduced by 52%, suggesting that CJ has a lesser impact on the bioavailability of S-warfarin. Intake of CJ 10 hours after warfarin—designed to avoid influencing absorption—resulted in a higher terminal-phase S-warfarin profile, while the R-warfarin profile remained unchanged. This suggests that CJ inhibited the elimination of S-warfarin, but not R-warfarin, a pattern similar to interactions observed between warfarin and metronidazole or cimetidine[38].

Comparison of pharmacokinetic parameters revealed that CJ increased the half-life and terminal exposure (AUC_{48-96}) of S-warfarin, confirming the inhibition of its elimination. This reduction in S-warfarin elimination caused by CJ may lead to an increased INR or even bleeding, which aligns with warnings reported in several clinical studies[39].

Subsequent pharmacodynamic evaluation revealed that INR was significantly elevated 24 hours after warfarin administration when CJ was ingested 10 hours later. This may reflect earlier clinical alerts about increased bleeding or INR elevation due to cranberry–warfarin interaction[39]. Combining the pharmacokinetic data, it is concluded that delayed ingestion of CJ increases INR by inhibiting the elimination of S-warfarin. In contrast, when CJ was consumed before warfarin, INR did not differ from the control.

Regarding the inhibition of S-warfarin elimination by delayed CJ ingestion, it was identified that polyphenols—metabolized into conjugates such as glucuronides and sulfates—inhibit the BCRP transporter, which may partly explain the reduced excretion of S-warfarin. This inhibition of BCRP by such conjugates is similar to the modulation observed with resveratrol metabolites[40]. It is hypothesized that delayed CJ intake may increase systemic exposure to various drugs that are BCRP substrates.

In the case of reduced absorption of S- and R-warfarin with concurrent CJ intake, it was suggested that CJ activates BCRP-mediated efflux, which may partly explain the reduced intestinal absorption of both warfarin enantiomers. Moreover, this innovative study employed cranberry-derived virtual molecules (CMs) to evaluate the modulation of drug-metabolizing enzymes by CJ. It was found that CMs inhibit CYP2C9, the primary enzyme responsible for metabolizing S-warfarin. This explains the reduced elimination of S-warfarin following delayed CJ ingestion. Although CYP1A2 and CYP3A4 activities were also inhibited by the CMs, no significant changes were observed in the pharmacokinetics of R-warfarin. Based on these findings, it is suggested that the pharmacokinetics, efficacy, and safety of other drugs that are substrates of CYP1A2, CYP2C9, or CYP3A4 may also be affected by cranberry[38].

This review highlights the complexity and clinical relevance of food–drug interactions. These interactions significantly impact the efficacy, safety, and adherence to treatment across various diseases, requiring close attention from healthcare professionals. They may occur, for instance, due to inhibition or induction of cytochrome P450 enzymes—responsible for drug metabolism—or due to interference with P-glycoprotein, which affects drug absorption and plasma levels.

Interactions between antihypertensive drugs and food can alter the bioavailability of medications, compromising blood pressure control and requiring strict monitoring, as well as specific dietary guidance to minimize adverse effects. These variations in drug efficacy underscore the importance of ongoing patient education to ensure blood pressure remains well-controlled.

In the case of nonsteroidal anti-inflammatory drugs (NSAIDs), food interactions influence their absorption and bioavailability, increasing the risk of gastrointestinal side effects. As such, the prescription and use of these drugs should take the patient's diet into account, adopting an integrated approach to mitigate potential risks.

Food interactions with antidepressants may compromise drug bioavailability by interfering with absorption and metabolism, which can delay treatment response or lead to drug accumulation, thereby increasing the risk of toxicity. Particularly, monoamine oxidase inhibitors (MAOIs) present potentially severe food interactions that can trigger serious adverse reactions, such as Stevens-Johnson syndrome—a rare and potentially fatal skin condition. Awareness of such interactions is essential

to ensure the efficacy and safety of antidepressant therapy.

Interactions between anticoagulants and food are also highly significant, as they can impair therapeutic efficacy and increase the risk of complications. Therefore, patients taking these drugs should be advised to maintain a balanced diet and avoid abrupt changes in the consumption of foods that may interfere with anticoagulant action.

In light of this, the training of healthcare professionals to manage and minimize the risks of these interactions is crucial. Enhancing clinical strategies in this regard will contribute to safer and more effective treatment of common conditions in the community, ultimately promoting public health and well-being.

AUTHOR CONTRIBUTIONS:

YMGA was responsible for the conception and design of the study, data analysis, and manuscript writing. LVAP carried out data collection, statistical analysis, and critical revision of the manuscript. MBA provided technical support, conducted the literature review, and performed the final revision of the text. All authors read and approved the final manuscript version and agree to take responsibility for its content.

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We wish to confirm that there are no known conflicts of interest associated with this publication and that no significant financial support has influenced its results.

DECLARATION REGARDING THE USE OF GENERATIVE AI:

The authors declare that generative artificial intelligence tools (such as ChatGPT, Grammarly, Deepseek, etc.) were not used in the preparation of the manuscript. However, the editorial board made the decision to utilize ChatGPT, an AI language model developed by OpenAI, for the translation of this manuscript from the original language, Portuguese, to English.

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