Evaluation of the labelling adherence of the food-associated effects of selected pharmacotherapy

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Abstract

Background: Pharmacotherapy and dietary interventions often work together to enhance patient treatment and outcomes. Yet, food-associated effects, including food-drug interactions, remain a significant challenge, especially for oral pharmacotherapy. These interactions can undermine the safety and efficacy of medications and negatively impact patients' nutritional status. Despite medicinal package inserts being the primary source of such information, studies from other countries highlight inconsistencies and inadequacies in the labelling of food-drug interactions. In South Africa, this critical issue remains largely unexplored, leaving potential risks unaddressed. The study aimed to evaluate the adherence of professional and patient information leaflets to labelling regulations concerning food-associated effects, providing some insight on a crucial yet often overlooked aspect of patient safety.

Methods: The South African Health Products Regulatory Authority (SAHPRA) labelling guidelines were used to evaluate the adherence to labelling of food-associated effects in the professional and patient information leaflets of warfarin, statins, fluoroquinolone and tetracycline antibiotics.

Results: The leaflets showed partial adherence to SAHPRA labelling guidelines. Food-drug interaction information was either lacking or inadequately described, particularly in relation to the mechanism of interaction, clinical outcomes, or recommendations. Although the information was mostly presented under appropriate headings, it was not always available under recommended sections and rarely cross-referenced.

Conclusions: The labelling of food-associated effects in the evaluated professional and patient information leaflets was partially adherent to SAHPRA labelling guidelines, which may hinder effective guidance for healthcare professionals and patients. Although a small sample, non-adherence is evident and suggests bolstering is needed to mitigate potentially clinically significant interactions.

Keywords: food-associated effects, food-drug interactions, labelling adherence, medicinal package inserts, patient information leaflets, professional information, South African Health Products Regulatory Authority

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Introduction

Food often constitutes an essential part of patients' therapeutic plans and healthy lifestyles.[1] Pharmacotherapy and dietary interventions often have complementary effects in healthcare practice.[2] However, food-associated effects, including food-drug interactions (FDIs), remain a challenge in patient treatment, especially for oral pharmacotherapy.[3] These effects include indirect and direct interactions between food and medications. For instance, food may indirectly alter medications' pharmacokinetic properties, for example, altering orally-administered medications' absorption by changing the gastrointestinal environment following a meal.[3] Conversely, food can directly interact with medications, where specific nutrients alter the medications' pharmacokinetics and/or pharmacodynamics, or medications can affect the patients' nutrient availability or nutritional status.[1,4]

Several studies highlight the clinical significance and implications of FDIs or food-associated effects.[1,4-6] Some food-associated effects may be beneficial to patients.[1,5] For instance, food can aid medications' absorption in the gastrointestinal tract.[5] However, some food-associated effects can be detrimental and result in therapeutic failure, or unexpected and exacerbated adverse effects of medications.[4,6] For example, calcium-rich foods can chemically complex with tetracycline or fluoroquinolone antibiotics, decreasing their gastrointestinal absorption, bioavailability and therapeutic outcomes.[7,8] Grapefruit juice inhibits atorvastatin[9] and simvastatin's CYP3A4-mediated metabolism, thus increasing their plasma levels and adverse effects, such as the risk of rhabdomyolysis.[10,11]

It is important that healthcare professionals (HCPs) have adequate information and work together in interdisciplinary teams to prevent or manage detrimental food-associated effects.[12-14] It is imperative that patients are provided with accurate and adequate information of food-associated effects to consider during therapy.[15] However, studies show that HCPs' and patients' knowledge of FDIs is inadequate.[12-16] Poor education and the unreliability of medicinal package inserts were identified as possible contributing factors, which may contribute to poor practices.[14,15] These include some HCPs not counselling patients on FDIs, and patients taking their medications with coffee or fruit juices which may predispose them to FDIs.[14,15]

In South Africa, a pivotal source of medication information are medicinal package inserts which contain professional information (PI) for HCPs, and patient information leaflets (PILs) for patients.[17,18] The PI is equivalent to the Summary of Product Characteristics (SmPC), a European document that informs HCPs how to administer medications safely and effectively.[17] The general regulations made in terms of the Medicines and Related Substances Act, 1965 (Act 101 of 1965), require a PI (Regulation 11) and PIL (Regulation 12) to accompany each medicine.[17,18] As such the South African Health Products Regulatory Authority (SAHPRA) requires pharmaceutical companies to include PIs and PILs in their applications when registering new medications (Regulation 16[3][g]).[17,18] According to SAHPRA labelling guidelines, PIs and PILs should contain adequate and comprehensive information of clinically significant FDIs and food-associated effects.[17,18] Therefore, if PIs and PILs meet their objectives, they aid HCPs in approaching healthcare from an informed perspective.[19]

Although other countries have reported labelling inconsistencies, such information in South Africa is lacking.[19-21] South African research thus far has focused on patients' and HCPs' knowledge, attitudes, and practices of FDIs in only one province.[13,15] Therefore, this study evaluated the labelling adherence of food-associated effects of selected pharmacotherapy in accordance with SAHPRA labelling guidelines.

Methods

The study obtained ethics approval from the Faculty of Health Sciences Research Ethics Committee (reference number: 248/2023). Four medications with clinically significant FDIs (warfarin, statins, tetracycline, and fluoroquinolone antibiotics) were selected, and their PIs and PILs sourced from SAHPRA's PI and PIL Repository.[22] To determine how general food-associated effects and FDIs information should be labelled in the PIs and PILs, two labelling guidelines were obtained from SAHPRA: Guideline for Professional Information for Human Medicines (Categories A and D) and the Guideline for Patient Information Leaflet for Human Medicines (Categories A and D).[17,18]

The guidelines were used to determine i) the sections that should contain food-associated effects information including clinically significant FDIs, and ii) the type of information that should be provided for clinically significant FDIs, and how it should be described. A focused search was conducted for each medicine via PubMed to create exemplars for comparison. To determine

Table I: The South African Health Products Regulatory Authority labelling guidelines for professional information and patient information leaflets reproduced verbatim from the guideline documents.

South African Health Products Regulatory Authority Guideline for Professional Information for Human Medicines (Categories A and D) SAHPGL-CEM-02_v5 2022[17]	
Sections that should contain food effects and food-drug interactions information	**Information that should be in the sections and how it should be presented**
Section 4.2: Posology and method of administration	The intake of the medicine in relation to fluid and food intake should be mentioned, with a cross-reference to Section 4.5 in case of specific interaction e.g. with alcohol, grapefruit, or milk.
Section 4.4: Warnings and precautions	In specific cases where the food-drug interactions are of major clinical importance, precautionary measures should be described in this section and cross-referenced to Section 4.5.
Section 4.5: Interaction with other medicines and other forms of interaction	Section 4.5 should be presented in the simplest way and a tabulated format may be used where there are numerous interactions. Information should include: • Relevant interactions with food or alcohol with a cross-reference from other sections; • Pharmacodynamic effects with a possibility of clinically significant potentiation or harmful additive effects; • Recommendations for clinically relevant interactions: ◦ Should state where concomitant use is not recommended (cross-reference to Section 4.4). ◦ Precautions including dose adjustment and specific situations where required (cross reference to Section 4.2 or 4.4). • Any clinical manifestations and effects on plasma levels and area under the curve of parent compounds or active metabolites and/or laboratory parameters; • Mechanism of interaction should be described if known; • Additional information on special populations should be given: ◦ If the impact of interaction is more severe in the elderly population, this should be stated. ◦ Food-drug interactions leading to a recommendation on co-administration with food should be specified whether they are relevant for paediatric use (especially newborns and infants whose diet is different, e.g. 100% milk).
South African Health Products Regulatory Authority Guideline for Patient Information Leaflet for Human Medicines (Categories A and D) SAHPGL-CEM-03_v7 2022[18]	
Section 2 under *with<food><and><drink><alcohol>*	• Should mention what the patient needs to know about food, drinks, and alcohol when taking the medicine. • Interactions not related to medicines should be mentioned here if reference is made in Section 4.5 of the professional information. • This section should not be used to tell patients whether their medicine should be taken before, during, or after meals as this should be addressed in section 3, but a cross-reference to Section 3 can be made.
Section 3 under *How to <take><use> the medicine*	Should state whether the medicine should be taken before or after meals.

adherence for labelling and description, the information found in PIs and PILs was compared to the exemplars following the SAHPRA guidelines.

Results and discussion

South African Health Products Regulatory Authority labelling guidelines

Table I provides an overview of the information necessitated for the PI and PILs. Food-associated effects information should be presented in three sections of the PI. Section 4.5 "Interaction with other medicines and other forms of interaction" should fully describe clinically significant FDIs.[17] This includes the mechanism of interaction, pharmacodynamic effects, clinical manifestations, effects on plasma levels and area under the curve (AUC), recommendations or precautions, and additional information on special populations.[17] For FDIs with major clinical relevance, precautionary measures should be described in Section 4.4 "Warnings and Precautions" with a cross-reference to Section 4.5.[17] Section 4.2 "Posology and Method of Administration" should address the intake of the medication in relation to food and fluid intake, where a reference should be made in Section 4.5 in cases of specific FDIs.[17] For the PIL, food-associated effects information should be presented in two sections of the PIL. Section 2 "With food, drink, and alcohol" should mention specific FDIs, provided that reference is made in Section 4.5 of the PI.[18] Furthermore, Section 3 should state whether the medication should be taken before or after meals.[18]

Labelling adherence of food-associated effects in SAHPRA-approved PIs and PILs

The presence of food-associated effects information in PIs and PILs

Eighteen medicinal products from the selected pharmacotherapy (four warfarin, seven statins, one tetracycline, and six fluoroquinolone medications) were sourced. All medications had PIs available, however, only 13 had PILs. For food-associated effects that result from indirect interactions between food and medications, the timing and administration of medications in relation to meal intake becomes important. The evaluated medications can be administered before or after meals. The majority (n = 9) of the PILs acknowledged that administration can occur before or after meals in Section 3. The selected medications can directly interact with certain foods/drinks.[7-10,23,24] As such, further analysis of the PIs and PILs focused on the specific FDIs of the selected pharmacotherapy.

While there are reports of other foods/drinks that can interact with the selected medications, this study only assessed the labelling adherence of the most common and clinically significant interactions between warfarin and vitamin K-containing foods, tetracyclines/fluoroquinolones and dairy products, and statins and grapefruit juice.[25,26] Although food-associated effects may result in clinically significant changes, studies report a lack of information not always mentioned in medicinal package inserts.[19-21,27-28] The study was in agreement with these reports as a few PIs (n = 6) and PILs (n = 3) completely lacked FDI information, highlighting a lack of adherence to SAHPRA guidelines in labelling clinically significant FDIs.[17,18]

The lack of labelling adherence is concerning, particularly for the medicinal samples used in this study. Warfarin, statins, tetracycline, and fluoroquinolone antibiotics are among the most studied and documented clinically significant FDIs.[26] Not labelling or insufficiently describing these medications' FDIs can hinder proper patient counselling, compromising safety and efficacy.[19]

The presentation of FDIs information under recommended sections and headings in PIs and PILs, as well as cross-referencing for PIs

While the presence of FDI information in PIs and PILs is important, so is the presentation under appropriate sections and headings.[17,18] Cross-referencing across the various sections avoids repetition of information, enabling HCPs or patients to easily navigate through the PIs and PILs.[17,18] The headings the FDIs were presented under were considered appropriate if they were specific (e.g. "*with<food><and><drink><alcohol>*"), bolded, and clear for the reader as stated by SAHPRA labelling guidelines.[17,18] The PIs (n = 18) and PILs (n = 12) provided the FDI information under appropriate headings, with one exception where a warfarin PIL did not mention the FDI information under the SAHPRA recommended heading "with<food><and><drink><alcohol>" in Section 2. The FDI was mentioned amidst other physiological aspects that can decrease the effect of warfarin, which could lead to it being overlooked. Furthermore, the FDI information in the PIs and PILs was not always presented in the recommended sections and rarely cross-referenced (Table II).

The presentation of FDIs in the recommended sections varied among the PIs and PILs. The majority (n = 11) of the PILs had the information present in Section 2. Although most of the PIs (n = 12) had FDIs information present in Section 4.5, only a minority (n = 4) contained FDIs information in Section 4.2 and Section 4.4. Only four PIs cross-referenced the information, however, inconsistently.

Inadequately describing FDIs hampers the effectivity of leaflets as a source of information.[19] Thus, PIs and PILs should adequately, comprehensively, and appropriately describe the information for HCPs and patients to enable proper patient counselling to prevent and treat FDIs.[19,20] According to the SAHPRA guidelines, a full description of a FDI entails the foods or drinks that interact with the medication, mechanism of interaction, clinical outcome, and recommendations to prevent the interaction.[17] However, as summarised below and detailed in Tables III and IV, a lack of adherence to SAHPRA labelling guidelines and inadequate description of FDIs information in the PIs and PILs were evident.

The description of FDIs information in warfarin, tetracyclines, fluoroquinolones, and statins PIs and PILs sourced from the SAHPRA website

Warfarin medicinal products

Foods such as green leafy vegetables, lettuce, broccoli, and spinach contain large amounts of vitamin K, which antagonises warfarin's

Table II: Presentation of food-drug interactions information in recommended sections, appropriate headings, and cross-referencing across the different sections of professional information and patient information leaflets. Green (sections contain the information, under appropriate headings, cross-referencing is applied for professional information), yellow (sections lack either one or more of the adherence measures), red (complete lack of adherence measures), grey (patient information leaflet not available).

Samples	Section 2 of PIL	Section 3 of PIL	Section 4.2 of PI	Section 4.4 of PI	Section 4.5 of PI
Warfarin					
Warfarin 1	• Information present • Inappropriate heading	• Information not present	• Information not present	• Information present • Appropriate heading • Cross-referencing applied	• Information present • Appropriate heading • Cross-referencing not applied
Warfarin 2	• PIL not available	• PIL not available	• Information not present	• Information not present	• Information not present
Warfarin 3	• Information present • Appropriate heading	• Information present • Appropriate heading	• Information not present	• Information present • Appropriate heading • Cross-referencing applied	• Information present • Appropriate heading • Cross-referencing not applied
Warfarin 4	• Information present • Appropriate heading	• Information present • Appropriate heading	• Information not present	• Information present • Appropriate heading • Cross-referencing applied	• Information present • Appropriate heading • Cross-referencing not applied
Statins					
Simvastatin 1	• Information present • Appropriate heading	• Information not present	• Information present • Appropriate heading • Cross-refencing not applied	• Information present • Appropriate heading • Cross-refencing not applied	• Information present • Appropriate heading • Cross-refencing not applied
Simvastatin 2	• Information present • Appropriate heading	• Information present • Appropriate heading	• Information not present	• Information not present	• Information present • Appropriate heading • Cross-refencing not applied
Simvastatin 3	• Information present • Appropriate heading	• Information present • Appropriate heading	• Information not present	• Information not present	• Information present • Appropriate heading • Cross-refencing not applied
Simvastatin 4	• PIL not available	• PIL not available	• Information not present	• Information not present	• Information not present
Simvastatin 5	• Information not present	• Information present • Appropriate heading	• Information not present	• Information not present	• Information not present
Atorvastatin 6	• Information present • Appropriate heading	• Information present • Appropriate heading	• Information not present	• Information not present	• Information present • Appropriate heading • Cross-referencing applied
Atorvastatin 7	• Information present • Appropriate heading	• Information present • Appropriate heading	• Information not present	• Information not present	• Information present • Appropriate heading • Cross-referencing not applied
Fluoroquinolones					
Ciprofloxacin 1	• PIL not available	• PIL not available	• Information not present	• Information not present	• Information not present
Ciprofloxacin 2	• PIL not available	• PIL not available	• Information present • Appropriate heading • No cross-referencing	• Information not present	• Information present • Appropriate heading • Cross-referencing not applied
Ciprofloxacin 3	• Information present • Appropriate heading	• Information present • Appropriate heading	• Information present • Appropriate heading • Cross-referencing applied	• Information not present	• Information present • Appropriate heading • Cross-referencing not applied
Ciprofloxacin 4	• PIL not available	• PIL not available	• Information not present	• Information not present	• Information present • Appropriate heading • Cross-referencing not applied
Levofloxacin 5	• Information not present	• Information present • Appropriate heading	• Information not present	• Information not present	• Information not present
Levofloxacin 6	• Information present • Appropriate heading	• Information not present	• Information not present	• Information not present	• Information not present
Tetracycline					
Tetracycline 1	• Information present • Appropriate heading	• Information not present	• Information present • Appropriate heading • Cross-referencing not applied	• Information not present	• Information present • Appropriate heading • Cross-referencing not applied

Table III: Document analysis of professional information for food-drug interactions information taken verbatim from the leaflets, where the exemplar provides the necessary information to which all other samples were benchmarked. Adherence measures for description: foods or drinks that interact with the medication, mechanism of interaction, clinical outcome, and recommendations/precautions. Green (adherence measure fully described), yellow (adherence measure partially described), red (complete lack of information).

Warfarin sample	Foods/Drinks	Mechanism of interaction	Clinical outcomes	Recommendations or precautions
Exemplar	**Vitamin K-containing foods (such as green leafy vegetables, lettuce, broccoli, and spinach)[23]**	**Vitamin K antagonises warfarin's vitamin K reductase inhibitory activity by facilitating clotting factor synthesis and activation[23]**	**The blood-thinning effect of warfarin is antagonised, leading to unstable coagulation[23] i.e. lowered prothrombin time (PT)[29]**	**Although completely avoiding these foods is not necessary, a consistent diet of vitamin K should be maintained while vitamin K dosage is closely monitored to avoid countering warfarin's anticoagulatory effect[29]**
Warfarin 1	Liver, broccoli, brussels sprouts, and green leafy vegetables contain large amounts of vitamin K	Mechanism not provided or explained	Anticoagulation control can be affected by sudden changes in diet	Patients should seek medical advice before making major diet changes
Warfarin 2	Information not provided	Information not provided	Information not provided	Information not provided
Warfarin 3	Liver, broccoli, brussels sprouts, and green leafy vegetables contain large amounts of vitamin K	Mechanism not provided or explained	Foods interacting with warfarin can affect prothrombin time, and anticoagulation control can be affected by sudden changes in diet	Patients should seek medical advice before making major diet changes
Warfarin 4	Liver, broccoli, brussels sprouts, and green leafy vegetables contain large amounts of vitamin K	Mechanism not provided or explained	Anticoagulation control can be affected by sudden changes in diet	Patients should seek medical advice before making major diet changes
Statin sample	**Foods/Drinks**	**Mechanism of interaction**	**Clinical outcomes**	**Recommendations or precautions**
Exemplar	**Grapefruit juice[9,10]**	**Grapefruit juice irreversibly inhibits CYP3A4-mediated pre-systemic metabolism of atorvastatin[9] and simvastatin[10]**	**Reduced metabolism increases the AUC and Cmax of atorvastatin[9] and simvastatin,[10] which increases the risk of statin-induced rhabdomyolysis[11]**	**Concomitant administration of large quantities of grapefruit juice (1 L daily) and these statins should be avoided or the dose of these statins should be reduced[9,10] to avoid rhabdomyolysis**
Simvastatin 1	Grapefruit juice	Grapefruit juice inhibits CYP3A4	Concomitant intake of large quantities of grapefruit juice (over 1 L daily) and 240 mL (in the morning) with the statin (in the evening) led to a 7-fold and 1.9-fold increase exposure to simvastatin, respectively, in previous studies	Patients should avoid the concomitant use of grapefruit juice and the statin
Simvastatin 2	Grapefruit juice	Grapefruit juice inhibits CYP3A4	Inhibition of CYP3A4 may result in high plasma levels of the statin (this is supported by findings from studies)	Patients should avoid the concomitant use of grapefruit juice and the statin
Simvastatin 3	Grapefruit juice	Grapefruit juice inhibits CYP3A4	Inhibition of CYP3A4 may result in high plasma levels of the statin increasing the risk of myopathy	Grapefruit juice is contraindicated, and patients should avoid the concomitant use of the statin and large quantities of grapefruit juice (more than 1L daily)
Simvastatin 4	Information not provided	Information not provided	Information not provided	Information not provided
Simvastatin 5	Information not provided	Information not provided	Information not provided	Information not provided
Atorvastatin 6	Grapefruit juice	Grapefruit juice inhibits CYP3A4	Inhibition of CYP3A4 can increase the plasma concentration of the statin	Grapefruit juice is contraindicated, and patients should avoid the combination of the statin and grapefruit juice
Atorvastatin 7	Grapefruit juice	Grapefruit juice inhibits CYP3A4	Inhibition of CYP3A4 can increase the plasma concentration of the statin	Patients should avoid the combination of the statin and grapefruit juice
Fluoroquinolone and tetracycline sample	**Foods/Drinks**	**Mechanism of FDI**	**Clinical effect on absorption and bioavailability**	**Recommendations or precautions**
Exemplar	**Calcium-rich foods such as dairy products or mineral-fortified drinks alone, (milk,[7,8] yoghurt,[8] calcium-fortified orange juice) [24]**	**Chemical complexation of fluoroquinolones or tetracyclines and calcium reduces their gastrointestinal absorption[7,8]**	**The chemical complexation with calcium reduces the absorption and bioavailability of fluoroquinolones[8] and tetracyclines[7]**	**Patients need to avoid calcium-rich foods for at least two hours before or after taking fluoroquinolones or tetracyclines[25]**
Ciprofloxacin 1	Information not provided	Information not provided	Information not provided	Information not provided
Ciprofloxacin 2	Calcium rich foods such as dairy products or mineral fortified drinks (milk, yoghurt, calcium fortified orange juice)	Mechanism of FDI not mentioned or explained	The interaction may reduce the absorption of the fluoroquinolone but dietary calcium as part of a meal does not significantly affect absorption	Patients should avoid concurrent use of these foods/drinks and the fluoroquinolone

Table III: *Continued*

Ciprofloxacin 3	Calcium rich foods such as dairy products or mineral fortified drinks (milk, yoghurt, calcium fortified orange juice)	Mechanism not mentioned or explained	The interaction may reduce the absorption of the fluoroquinolone but calcium as part of a meal does not significantly affect absorption	Patients should avoid concurrent use of these foods/drinks and the fluoroquinolone
Ciprofloxacin 4	Calcium rich foods such as dairy products or mineral fortified drinks (milk, yoghurt, calcium fortified orange juice)	Mechanism not mentioned or explained	The interaction reduces the absorption of the fluoroquinolone but calcium as part of a meal does not significantly affect absorption	Patients should avoid concurrent use of these foods/drinks and the fluoroquinolone
Levofloxacin 5	Information not provided	Information not provided	Information not provided	Information not provided
Levofloxacin 6	Information not provided	Information not provided	Information not provided	Information not provided
Tetracycline 1	Milk	Mechanism not mentioned or explained	Clinical effect not mentioned	Patients should avoid the concomitant use of the tetracycline and milk. Milk should not be taken within two hours before or after taking the tetracycline

vitamin K reductase inhibitory activity by facilitating clotting factor synthesis and activation.[23] As such, warfarin's anticoagulant properties are pharmacodynamically antagonised, leading to unstable coagulation,[23] as seen by the lowered prothrombin time.[28] Completely avoiding these foods is not necessary, but to ensure therapeutic efficacy, patients should maintain a consistent diet of vitamin K while HCPs closely monitor its dosage.[28]

Of the four warfarin samples, all had PIs, while only one lacked a PIL. The FDI's information was found in three out of four PIs, and in all three PILs. While interacting foods and the lack of anticoagulant control were mentioned in all, none of them described the mechanism of interaction. Inconsistent description of how prothrombin time, bleeding time or coagulation were altered by dietary changes was observed.

All three PIs and PILs advised that patients should seek medical advice before making major diet changes. However, the recommendation lacked the specific and detailed precautions that HCPs should advise patients to take. Therefore, the recommendation might be ineffective in situations where the HCPs are not fully informed about this interaction. Couris et al. reported inadequate knowledge of warfarin-vitamin K interactions among HCPs.[16] If PILs advise patients to consult HCPs, while their PIs lack the full description and recommendations pertaining to this FDI, that could lead to improper patient counselling, subsequently, resulting in warfarin therapeutic failure or adverse medical repercussions such as haemorrhagic complications.[16,26]

Fluoroquinolone and tetracycline antibiotics medicinal products

Calcium-rich foods such as dairy products or mineral-fortified drinks alone (milk, yoghurt, calcium-fortified orange juice) can interact with fluoroquinolones and tetracyclines as the chemical complexation of these medications and calcium reduces their gastrointestinal absorption and bioavailability.[7,8,24] Therefore, patients need to avoid calcium-rich foods for at least two hours before or after taking fluoroquinolones and tetracyclines.[25]

The reduced absorption and bioavailability of fluoroquinolones can lead to reduced therapeutic efficacy or even antibiotic resistance, predisposing patients to treatment failure.[4] However, out of all the medicinal samples, FDI's labelling adherence was poorer for fluoroquinolones. Of seven PIs assessed (six fluoroquinolones and one tetracycline), only three fluoroquinolone PIs and the tetracycline PI contained FDI information. Four PILs were available on the SAHPRA website (three fluoroquinolones and one tetracycline), and only one fluoroquinolone and the tetracycline PIL contained FDI information. All the fluoroquinolone samples listed the interacting foods and drinks. Concerningly, the tetracycline sample only mentioned milk, which may lead to the misconception that patients can take the medication with other dairy or calcium-containing products not mentioned.

Similar to the warfarin samples, the mechanism of interaction was lacking in all PIs and PILs. The fluoroquinolones' PIs mentioned that the interaction may reduce absorption, while this information was lacking in the tetracycline PI. While some PIs and PILs recommended that patients should avoid concurrent use of these foods or drinks with the medications, only a minority (one PI and two PILs) mentioned specific timing recommendations, such as taking the medications two hours before or after consuming the foods/drinks.

Statin medicinal products

Grapefruit juice irreversibly inhibits the CYP3A4-mediated-presystemic metabolism of statins (simvastatin and atorvastatin), increasing their AUC, maximum plasma concentration (Cmax), and the risk of rhabdomyolysis.[9-11] Therefore, the concomitant administration of large quantities of grapefruit juice (1 L) alongside these statins should be avoided, or the dose of the statins should be reduced to avoid rhabdomyolysis.[9,10]

Of the seven statin samples, all had PIs, while only one lacked a PIL. The FDIs information was found in five PIs and PILs and grapefruit juice was mentioned in all. CYP3A4 inhibition or induction is one of the most commonly documented pharmacokinetic interactions and a major consideration in the safe and effective use of statins.[20] However, similar to Saito et al., the mechanism of interaction was

Table IV: Document analysis of patient information leaflets for food-drug interactions information taken verbatim from the leaflets, where the exemplar provides the necessary information to which all other samples were benchmarked. Adherence measures for description: foods or drinks that interact with the medication, clinical outcome, and recommendations/precautions. Green (adherence measure fully described), yellow (adherence measure partially described), red (complete lack of information).

Warfarin sample	**Foods/Drinks**	**FDI clinical effects**	**Recommendations and precautions**
Exemplar	**Vitamin K-containing foods (such as green leafy vegetables, lettuce, broccoli, and spinach)[23]**	**The blood-thinning effect of warfarin is antagonised leading to unstable coagulation,[23] i.e. lowered prothrombin (INR) time[29]**	**Although completely avoiding these foods is not necessary, a consistent diet of vitamin K should be maintained while vitamin K dosage is closely monitored to avoid countering warfarin's anticoagulatory effect[29]**
Warfarin 1	Liver, broccoli, brussels sprouts, and green leafy vegetables contain large amounts of vitamin K	Vitamin K-containing foods decrease the effect of warfarin	Patients should not make any major changes to their diets while taking the warfarin
Warfarin 2	PIL not available	PIL not available	PIL not available
Warfarin 3	Liver, broccoli, brussels sprouts, and green leafy vegetables contain large amounts of vitamin K	Sudden changes to diet can affect the patient's bleeding time	Patients should seek medical advice before undertaking any major changes in their diet
Warfarin 4	Liver, broccoli, brussels sprouts, and green leafy vegetables contain large amounts of vitamin K	Sudden changes to diet can affect the patient's bleeding time	Patients should seek medical advice before undertaking any major changes in their diet
Statin sample	**Foods/Drinks**	**FDI clinical effects**	**Recommendations or precautions**
Exemplar	**Grapefruit juice[9,10]**	**Reduced metabolism increases the AUC and Cmax of atorvastatin[9] and simvastatin,[10] which increases the risk of rhabdomyolysis[11]**	**Concomitant administration of large quantities of grapefruit juice (1 L daily) and these statins should be avoided, or the dose of these statins should be reduced[9,10] to avoid rhabdomyolysis**
Simvastatin 1	Grapefruit juice	Grapefruit juice contains one or more components that alter how the body uses the statin	Consuming grapefruit should be avoided
Simvastatin 2	Grapefruit juice	There is an interaction with CYP3A4 inhibitors and there may be a similar interaction with grapefruit juice	Recommendations or precautions not given
Simvastatin 3	Grapefruit juice	Grapefruit juice can prevent the body from breaking down the statin, increasing the risk of the muscle side effects of unexplained muscle pain, tenderness, or weakness	Patients should avoid large quantities of grapefruit juice (more than 1L daily)
Simvastatin 4	PIL not available	PIL not available	PIL not available
Simvastatin 5	Information not provided	Information not provided	Information not provided
Atorvastatin 6	Grapefruit juice	Grapefruit juice and the statin could lead to an undesirable interaction	The combination of grapefruit juice and the statin should be avoided
Atorvastatin 7	Grapefruit juice	Grapefruit juice can interact with the satin	Patients should not take the statin if they drink excessive amounts of grapefruit juice regularly
Fluoroquinolone and tetracycline sample	**Foods/Drinks**	**FDI clinical effects**	**Recommendations or precautions**
Exemplar	**Calcium-rich foods such as dairy products or mineral fortified drinks alone (milk,[8] yoghurt,[8] calcium fortified orange juice[24])**	**The chemical complexation with calcium reduces the absorption and bioavailability of fluoroquinolones[8] and tetracyclines[7]**	**Patients need to avoid calcium-rich foods for at least two hours before or after taking fluoroquinolones or tetracyclines[25]**
Ciprofloxacin 1	PIL not available	PIL not available	PIL not available
Ciprofloxacin 2	PIL not available	PIL not available	PIL not available
Ciprofloxacin 3	Dairy products (milk and yoghurt) and calcium-fortified juices	Large amounts of dairy products particularly milk or yoghurt may slow down the uptake of the fluoroquinolone	Patients should not take the fluoroquinolone with dairy products or calcium- fortified juices and recommend that the fluoroquinolone should be taken 1 to 2 hours before or at least 4 hours after these foods
Ciprofloxacin 4	PIL not available	PIL not available	PIL not available
Levofloxacin 5	Information not provided	Information not provided	Information not provided
Levofloxacin 6	Information not provided	Information not provided	Information not provided
Tetracycline 1	Milk	The absorption of the tetracycline is not affected by moderate amounts of milk	Recommendations or precautions to prevent the FDI are not given

described by only one PI and PIL.[20] Moreover, both in this analysis and that of Saito et al., no information on AUC changes were noted, with a rare mention on the effect on Cmax and increased risk of rhabdomyolysis.[20]

In addition to the inadequate description of the FDI, a lack of or inadequate description of recommendations was observed in some of the PIs and PILs. The PIs and PILs advised against the concomitant use of the statins and grapefruit juice, with one exception where excessive grapefruit juice drinkers were advised not to use the statin. However, only one PI and PIL mentioned the quantity of grapefruit juice to be avoided, making this recommendation ineffective in situations where HCPs and patients lack the same information.

Overall, the PIs and PILs did not meet SAHPRA labelling requirements, both in quantity and quality, potentially due to various factors. One possible factor is the source references used for PIs during the registration process. SAHPRA labelling guidelines state that peer-reviewed journals, the most recently approved innovator SmPC/PI from a recognised regulatory authority, or the most recent SAHPRA-approved innovator PI can be used as source references.[17] The PubMed-focused search for the FDIs of warfarin, statins, fluoroquinolones, and tetracycline showed that these interactions are fully described in the literature.[17] However, the evaluated PIs and PILs had inadequate information and often displayed similar word-for-word inconsistencies. For example, all warfarin PIs did not mention how HCPs should prevent the interaction and only advised patients to seek medical advice, whereas PIs should include detailed guidance for HCPs. These inconsistencies suggest that pharmaceutical manufacturers may rely heavily on other approved PIs or SmPCs. San Miguel et al. also reported SmPCs to be a suboptimum source of FDIs information.[19] Therefore, using recently approved PIs or SmPCs as the only source of labelling FDIs may result in a cycle of unresolved inconsistencies. Pharmaceutical companies are advised to not only source FDI's information from already approved PIs or SmPCs, but to also confirm with peer-reviewed journals.

In addition to source references for labelling FDIs, the approval dates of the PIs and PILs, and the overall approval process by regulatory authorities are notable factors to consider. Labelling guidelines for PIs and PILs have been in place since the early 2000s under the Medicines Control Council (MCC), with the transition to SAHPRA in 2019 introducing the first set of SAHPRA-specific guidelines. Of the evaluated PIs (n = 18) and PILs (n = 13), eight PIs and four PILs were approved under MCC, while the remaining ten PIs and nine PILs were approved under SAHPRA. Notably, the year of approval might have influenced the absence of FDI's information. The majority of the leaflets that lacked FDI information (five PIs and two PILs) were approved before 2019, while a minority (one PI and one PIL) were approved after. However, discrepancies in the description of FDIs persisted in the majority of the PIs (n = 11) and PILs (n = 9), regardless of their approval dates. These findings highlight a need for SAHPRA to ensure compliance to labelling guidelines and to ensure that PIs and PILs are consistently updated to address any FDI information discrepancies, thereby meeting current standards. Addressing these gaps is crucial, as ineffective labelling of FDI information can impact the safety and efficacy of medications.

The study findings align with those of San Miguel et al, suggesting that the inadequate labelling of FDI information in medicinal package inserts may reflect a broader issue where regulatory and pharmaceutical practices overlook the importance of FDIs.[26] Acknowledging the lengthy process of medicine registration, including the proposal of PIs and PILs by pharmaceutical companies and their assessment and approval by regulatory authorities, there is potential for improvement in addressing these gaps.[17,18]

Limitations of the study

The small sample size used for the selected PIs and PILs was a limitation and thus the study findings may not be generalisable to all existing PIs and PILs. However, along with literature findings, the analysis of the PIs and PILs highlighted non-adherence and inconsistencies in the labelling of food-associated effects especially FDIs, which may impact healthcare practice.

Conclusion

The study highlights that although the impact food has on medications' efficacy is acknowledged, it is often understated in the PIs and PILs. Studies show that food-associated effects information, especially that of FDIs, is not always present in medicinal package inserts. Furthermore, if it is present, the FDIs information is often inadequately described. The conducted study also showed a lack of and inadequate description of FDIs in PIs and PILs of warfarin, statins, tetracycline, and fluoroquinolone antibiotics. Moreover, PIs and PILs did not always describe FDI information in the recommended sections and cross-referencing was rarely applied. Thus, the PIs and PILs of the selected pharmacotherapy were partially adherent to the SAHPRA labelling guidelines. The absence of FDI information in medicinal package inserts makes them an impracticable source of such information for HCPs, which may impact optimal patient counselling. Therefore, it is recommended that pharmaceutical companies and regulatory authorities work together to improve adherence to SAHPRA labelling guidelines. Due to the long regulatory procedures that surround the update of PIs and PILs information, it is recommended that future studies investigate other educative methods. Access to adequate FDIs or any food-associated effects information will allow HCPs and patients to prevent clinically significant FDIs or any food-associated effects, resulting in the safe and effective use of medications and food.

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Conflict of interest

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