RESEARCH ARTICLE

Analysis of drug-food interactions in inpatient treatment: A university hospital case

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Summary

Patients' nutrition during inpatient treatment can reduce the pharmacodynamics of drugs. Therefore, monitoring of drug-nutrient interactions is essential for patient safety. Pharmaceutical Data Banks (PDB) databases provide information regarding potential drug-drug, drug-food, and drug-allergy interactions. When Clinical Decision Support Systems (CDSS) are integrated with PDBs, drug-drug and drug-allergy interactions can be prevented when physicians prescribe drugs and when pharmacists evaluate those prescriptions. However, nutrition planning is done by dieticians, and it is not common practice for dieticians to use CDSSs integrated with PDB to access patient prescription information. This study aims to measure drug-food interactions in hospitals where physicians and pharmacists use CDSSs integrated with PDBs. For the most part, dieticians plan patient diets according to the patient's primary disease (diabetes, etc.) and do not access prescription data. We cooperated with a university hospital in Turkey, accredited by HIMSS in 2017 at EMRAM Stage 6, to monitor hospitalized patients for at least one week in 2018. According to the findings, it was determined that 1,451 different drugs were administered 1,620,573 times to a total of 27,455 patients. It was determined that eight (0.55%) different drugs administered to 581 (2.1%) of the patients could interact with food and that these eight drugs were prescribed 8,089 times (0.49%) during the observation period. Although some drug-nutrient interactions were documented due to the study, the number of detected and documented interactions and their severity were relatively low. Precautions taken by dieticians, such as completely removing certain nutrients, like grapefruit, from the diet list, seem to be effective in preventing common interactions. To eliminate drug-nutrient interactions, it will be beneficial for dieticians to access patients' prescribing information and use the CDSS integrated with PDB.

Keywords: Drug-Food Interaction, Pharmaceutical Data Bank, Clinical Decision Support Systems, HIMSS, EMRAM

INTRODUCTION

Risk Factors of Drug Interactions

According to the World Health Organization definition, medicine is a substance or product used or intended to change or examine physiological systems or pathological conditions for the benefit of the user[1]. The expected effectiveness of drugs depends on many factors. Unexpected or undesired side effects may develop during the use of drugs[2]. Toxic effects, allergic reactions, or drug interactions have a negative effect on the drug's effectiveness. Conditions that can reduce the expected effectiveness of the drug and threaten the patient's health are as follows:

- Drug-Drug Interactions
- Drug-Food Interactions
- Drug-Allergy Incompatibility
- Drug-Laboratory Result Incompatibility
- Dose Incompatibility (Maximum Dose, Cumulative Dose, Pediatric Dose)

In a 2009 study on drug allergies, patients admitted due to drug reactions constituted 6.5% of all hospital admissions and adverse drug reactions, which prolonged the hospital stays of 15% in inpatient[3].

Pharmaceutical Data Bank Use in Clinical Decision Support Systems

Clinical Decision Support Systems (CDSS) are information systems that help healthcare providers in clinical diagnosis, treatment, care, and rehabilitation stages by combining patient electronic health record (EHR) data with evidence-based scientific information[4]. Pharmaceutical Data Banks (PDB) contains information about potential drug-drug, drug-food, drug-allergy, and drug-clinical indicator incompatibilities and are used as a reference for the rules in drug-related CDSSs. In this way, CDSSs of hospital information systems (HIS) can issue warnings and reminders during physician prescription orders and pharmacist prescription approvals. In another study conducted in the United States in 2010, it was determined that CDSSs reduced medication errors by 81% and severe drug errors by 86%[5]. Another study in 2011 showed that one of the most important causes of complications during the treatment process, medication errors, occurred for 6.5% of adult inpatients and 27.4% of outpatients[6]. Studies on PDBs and drug interactions date back to a study conducted in 1997, which observed that 173 patients (6.8%) were prescribed drugs at risk for drug-drug interaction[7]. Drug-drug interactions are a critical issue in terms of patient safety at the prescribing stage. Prescriptions written in primary health care institutions were examined in a study conducted between 2006 and 2007. In this study at 15 primary health care institutions, it was observed that the PDB reduced the drug-drug interactive prescribing rate by 17%[8].

CDSSs can also encourage nurses to administer drugs on time. In one study, 7,323 drug administrations performed without using an electronic drug administration system and 7,318 drug administrations performed using an electronic drug administration record integrated with CDSS were observed over 2-4 weeks. The results obtained in the study showed that, with the use of electronic drug administration records, wrong drug administrations were decreased by 54.4%, wrong dosing applications by 41.9%, documentation errors by 80.3%, total drug errors by 25.1%, and adverse drug events by 11.1%[9]. Similarly, in a study conducted by Silveira et al. to measure electronic prescription systems' effect on medication errors, it was found that medication errors were reduced by 78% during the treatment process[10].

Drug - Food Interaction

The physical, chemical or physiological relationship between drugs and foods, nutrients, or herbal extracts is defined as drug-food interaction[11,12]. Drug-food interactions can reduce treatment effectiveness due to a decrease in the drug's bioavailability, resulting in side effects or an increase in the drug's bioavailability that may result in toxicity[11]. Therefore, in addition to the widely accepted five-rights rule (right patient, right medication, right time, right dose, right route) of medication administration[13], drug-food interactions should also be taken into account to improve patient safety[14].

Effects of Drugs on Nutritional Status

It is essential to consider medications administered to a patient when planning meals during inpatient treatments. The drug groups that most commonly interact with food are anesthesia drugs, antibiotics, pain relievers, antifungal drugs, antiretroviral drugs, anticholinergic drugs, antispasmodic drugs, antitumor drugs, antidiabetic drugs, antituberculosis drugs, antihistamines, antihypertensives, asthma drugs, hormones, osteoporosis drugs, diuretics, triglyceride, and cholesterol-reducing drugs, heartburn and ulcer drugs, laxatives, psychiatric drugs, hypnotic drugs, sedative drugs, and anticonvulsant drugs[15]. The most basic types of drug-food interactions are shown in Figure 1.

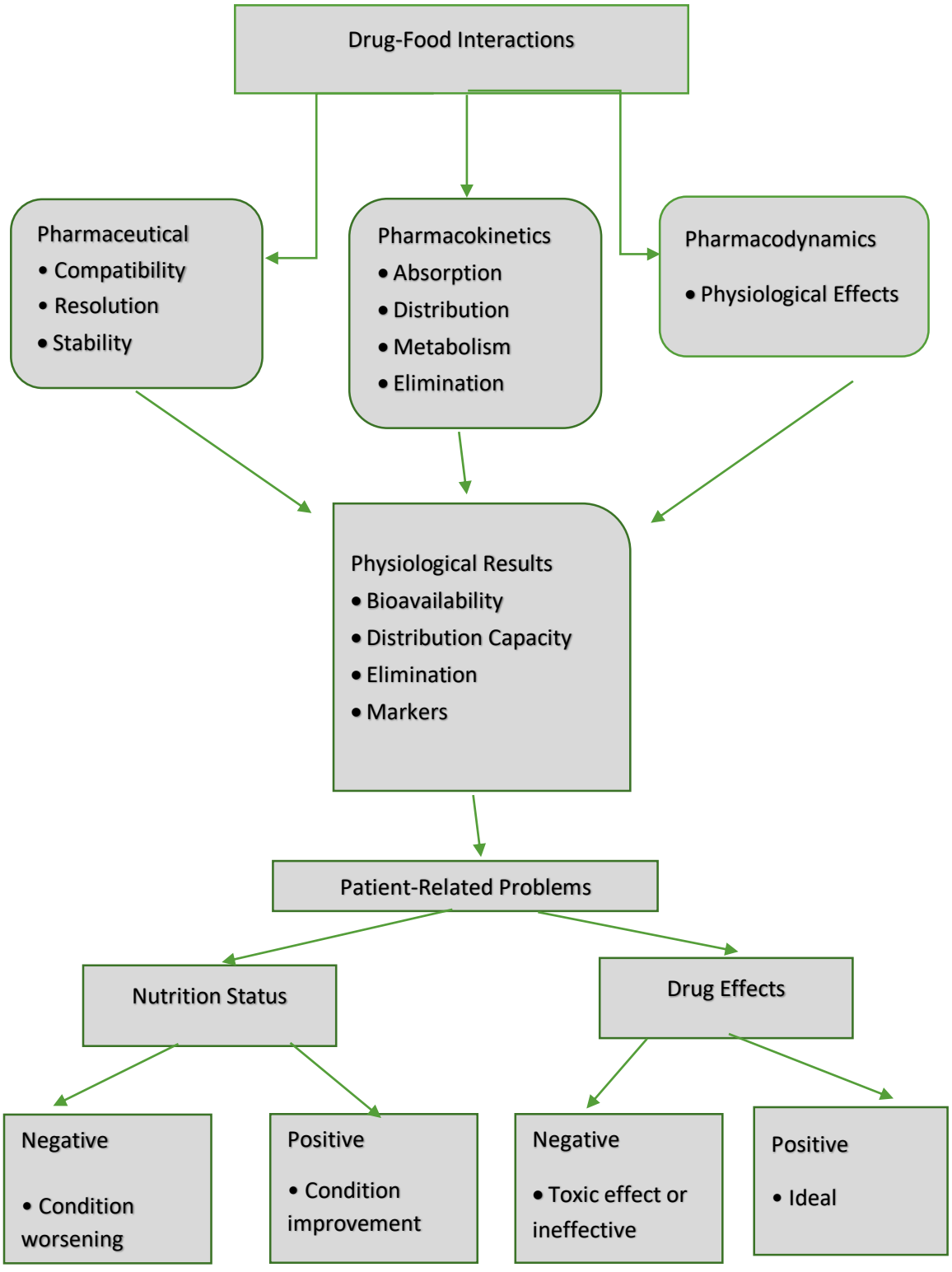

Figure 1 Drug-Food Interactions Diagram [16] *(Adapted from the source.)*

To prevent drug-food interactions and reduce risk, drug administration's recommended time is 1 hour before or 2 hours after food intake[17]. Generally, drug-food interactions do not cause clinically severe interactions. Still, they reduce the effect of drugs with narrow therapeutic ranges and drugs that require dose control, which can prolong the treatment process or cause adverse events[18].

Although few studies in the literature provide concrete evidence that drug-food interactions can have serious outcomes, there is some indication that drug-food interactions can be fatal. In an article on drug interactions published in 2003, a study of 12 subjects was shared. Prolonged treatment was observed in electrocardiogram QT intervals of patients who ingested grapefruit juice and *terfenadine* together. That indicates that the consumption of grapefruit juice and the drug *terfenadine* together can lead to fatal cardiac arrhythmia[19]. Therefore, dieticians must coordinate with clinicians and pharmacists while planning patient meals to optimize drugs' clinical efficacy and reduce potential risks[20].

Dietician responsibility for drug-food interaction

Dieticians are defined as "health professionals that plan patient diet programs according to the composition of natural and therapeutic foods, which is suitable for medical and surgical treatments in congenital and acquired diseases and other special cases, and plan and provide training."[21]. Job descriptions of dieticians reveal that dieticians should coordinate with physicians, pharmacists, and nurses. In practice, however, it is observed in many hospitals that the dietician only has information about the patient's primary disease (e.g. diabetes, hypertension, etc.) and prepares the patient diet according to this disease's essential requirements. In such cases, dietitians do not have sufficient data on the drugs administered to the patient or use PDBs.

In this study, potential drug-food interactions will be investigated by looking at diets prepared by dieticians who only have access to the admitted patient's primary diagnostic information, do not use any PDBs, and do not have access to information regarding prescribed drugs or drugs administered to the patient.

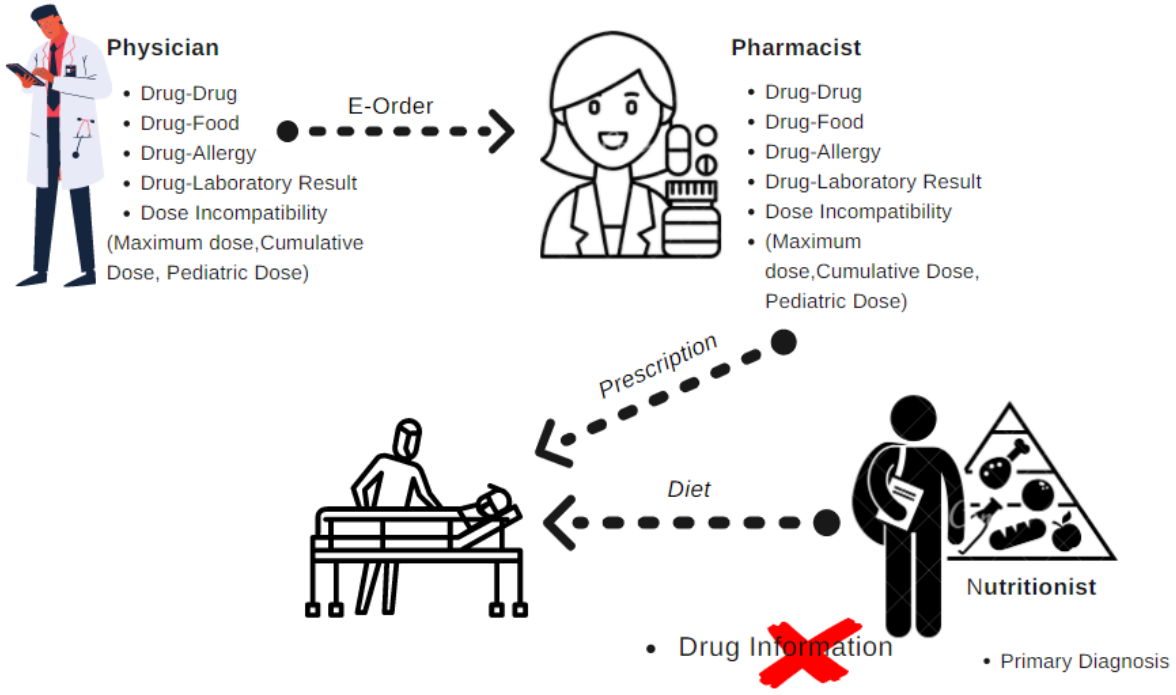

Figure 2 Medication and Diet Planning Process

METHOD

The data set for this study consists of medical records of hospitalized patients for at least one week during the year 2018 in a university hospital with 515 beds in Istanbul. This hospital is one of the stage 6 hospitals validated against HIMSS (Healthcare Information and Management Systems Society) EMRAM (Electronic Medical Record Adoption Model) criteria (24). The patients' identifying information was hidden from the researchers so that only the protocol number, drug order information, and daily diet lists were accessible.

When physicians issue electronic prescriptions in the hospital examined in this study, they utilize a PDB (vademecum)[22] and an academic database (uptodate)[23]. Pharmacists use these same resources during the prescription review and approval process.

Once patients' prescription data were obtained, researchers identified detailed pharmacological information for each drug administered during their inpatient stay. The Drug-food interaction information was obtained using the vademecum PDB's on-line service[22]. Drug-food interaction warnings are classified according to food types (high fiber, high fat, sucrose, dairy, fruit juice, etc.).

Researchers also accessed patient prescribed meals on the hospital's Nutrition Information Systems (NIS) module in the HIS for each patient in the data set. Each meal in the diet was matched with the food types with risk for drug-food interaction. In this way, the food types and drugs ingested by patients on the same day were analyzed to identify potential drug-food interactions.

All the data tables obtained were transferred to the Qlikview[24] Personnel Edition version

(used free of charge) to quickly and multidimensionally visualize and analyze it.

RESULTS

A total of 27,455 patients hospitalized during the 2018 review period were administered 1,451 different drugs 1,620,573 times. It was found that eight (0.55%) different drugs administered to 581 (2.1%) patients had potential food-drug interactions, and these drugs were prescribed 8,089 times (0.49%), as shown in Table 2.

Table 2. Drugs that can interact with food and the number of prescriptions

Drugs	Number of Prescriptions
AMIKAVER 100 MG/2 ML AMPUL	5.908
AMIKAVER 500MG/2 ML AMPUL	1.221
AMIKETEM 500 MG/2 ML AMPUL	125
ANDAZOL 400 MG TABLET	24
BENIPIN 4 MG FILM TABLET	336
DAROB 80 MG TABLET	447
GLUCOBAY 50 MG TABLET	26
GLUCOBAY 100 MG TABLET	2
Total	**8.089**

The food types that can potentially interact with the drugs prescribed to the patients and the number of prescriptions in the data set are shown in Table 3.

Table 3. Food types that can interact with drugs given to patients and the number of prescriptions for drugs

Food Types	Number of Drugs with Interaction Potential*	Number of Prescriptions for Drugs with Interaction Potential	Number of Patients with Interaction Potential
Grapefruit juice	1	336	82
Fibrous foods	2	4.175	244
Foods containing sucrose	2	28	4
Dairy products	3	3.526	250
Fatty foods	1	24	1
Total	**9**	**8.089**	**581**

** Some drugs have more than one food interaction*

When we compare physician-prescribed drugs with dietician-prescribed meals, it was found that drugs with drug-food interaction potential were administered 146 times on the same day that foods containing fiber, dairy, fatty foods, or sucrose-containing foods were given to patients. This number corresponds to 1.8% of the total drugs with the potential to interact and 0.009% of the total of all prescribed drugs. These findings are detailed below according to food type

Grapefruit Juice
In total, 336 drugs that were administered to patients can potentially interact with grapefruit juice. There was no grapefruit found on the hospital menu or in dietician prescribed meal plans, so there was no opportunity for a drug-food interaction for this food type.

Fatty Foods
During the study in 2018, there was no indication that patients were administered fatty foods that could interact with physician-prescribed drugs on the same day.

Fibrous Foods
During the study period, patients were administered drugs incompatible with pectin and other soluble fibrous nutrients on the same day they were given dietician prescribed diets containing those foods a total of 71 times. The drugs with potential fatty food interactions that may put the patients at risk for slow drug absorption are listed in Table 4.

Table 4. Drugs that interact with fibrous foods and the number of prescriptions

Drugs	Number of Prescriptions
AMIKAVER 100 MG/2 ML AMPUL	47
AMIKAVER 500MG/2 ML AMPUL	24
Total	**71**

Dairy Products
During the study period, patients were given meals containing dairy products and drugs that are incompatible with dairy products on the same day a total of 67 times. Each time, the patient was at risk for decreased treatment effectiveness due to reduced absorption of drugs due to the casein and calcium found in dairy products. These drugs are specified in Table 5, with the number of prescriptions found in the data set.

Table 5. Drugs interacting with dairy products and the number of prescriptions

Drugs	Number of Prescriptions
AMIKAVER 100 MG/2 ML AMPUL	47
DAROB 80 MG TABLET	20
Total	**67**

Foods Including Sucrose
During the study period, patients were given incompatible drugs with sucrose and meals containing sucrose on the same day eight times. Each time potentially affected the absorption rate of the drug by delaying carbohydrate passage from the intestine. The drugs mentioned above are specified in Table 6 with the number of prescriptions.

Table 6. Drugs interacting with sucrose and the number of prescriptions

Drugs	Number of Prescriptions
GLUCOBAY 50 MG TABLET	8
Total	**8**

As a limitation of our study, we should state that the exact times that drugs and foods were administered could not be obtained, so same-day administrations identified potential risks. If there were at least two hours between administering drugs and meals on the same day, a drug-food interaction was unlikely to occur.

DISCUSSION

Although some potential drug-food interactions were identified as a result of the study, the number of potential interactions detected and their potential effects were relatively low. In this study, the use of a pharmaceutical data bank by the physician prescribed and pharmacist reviewed drug was considered as a tool to increase drug safety. However, the main factor influencing identifying potential drug-food interactions is the dietician's access to the patient's EHR, especially the patient's prescription information. At the hospital where the study was conducted, dieticians accessed the patients' primary diagnosis (diabetes, hypertension, etc.) and prescribed patient diets accordingly. However, dieticians did not access the patients' drug prescription information and did not use a CDSS supported by a pharmaceutical data bank. When we evaluate the results of 100 studies conducted in 2005, it says that CDSS increased the practitioners' performance[25]. A study conducted in 2012 states the following about CDSSs and drug databases; CDSSs shorten the process with information support and make it practical, as well as significantly increasing patient safety because it is said that the risk of medication error will decrease in the prescribing process when CDSS is used with routine e-order[26].

Nevertheless, measures such as removing certain foods, like grapefruit, which can potentially interact with drugs from the hospital diet list entirely, are practical ways to reduce drug-food interactions. Studies show that even a glass of grapefruit juice shows negative interactions. It also suggests that the interaction starts 30 minutes after drinking, and the effect lasts for three days[27]. Studies with many food groups such as grapefruit juice are also available. For example, interaction has been found between the Warfarin drug and pomegranate juice[28]. It should always be kept in mind that possible nutrients such as these may reduce the interaction. Additionally, providing dieticians with access to disease diagnoses and prescribed drugs their potential drug-food interactions using a PHD-supported CDSS can prevent cases of drug-nutrient interactions.

In 1995, a study conducted with 834 family physician assistants in 56 specialization programs looked at physician attitudes and knowledge about drug-food interactions. Most physicians stated that they received little or no training on drug-food interactions during medical school (83%) and residency (80%) training. While 79% of the physicians believed that informing patients about drug-food interactions was the physician's responsibility, 75% thought pharmacists were responsible for drug-food interactions, and 66% thought it was the dietician's responsibility[29]. Accordingly, physicians do not see themselves as sufficient in terms of preventing drug-food interactions. At least at the perception level, they think that responsibility for preventing drug-food interactions is distributed among physicians, pharmacists, and dieticians. Our study indicates that the use of PDB supported CDSSs by physicians, pharmacists, *and* dieticians help plan the patient's food and drug prescriptions to minimize drug-food interaction cases.

References

1. Karadakovan A. İlaç Etkileşimleri ve Hemşire Sorumlulukları. *Ege Üniversitesi Hemşirelik Yüksek Okulu Derg*. 1994;10:5-7.
2. Şensoy F, Özaydın FN. Besin-İlaç Etkileşimleri. In: *Hastalıklarda Beslenme Tedavisi*. ; 2017:981-1013.
3. Mirakian R, Ewan PW, Durham SR, et al. BSACI guidelines for the management of drug allergy. *Clin Exp Allergy*. 2009;39(1):43-61. doi:10.1111/j.1365-2222.2008.03155.x
4. Koç E, Atılgan Şengül Y, Uyar Özkaya A, Gökçe B. Klinik Karar Destek Sistemleri Kullanımına Yönelik Bir Araştırma: Acıbadem Hastanesi Örneği. *ıx Ulus Tıp Bilişim Kongresi*. 2012:64-74.
5. Forni A, Chu H, Fanikos J. Technology Utilization to Prevent Medication Errors. *Curr Drug Saf*. 2009;5:13-18. doi:10.2174/157488610789869193
6. Lu CY, Roughead E. Determinants of patient-reported medication errors: a comparison among seven countries. *Clin Pract*. 2011;(16):733-740. doi:https://doi.org/10.1111/j.1742-1241.2011.02671.x
7. P. E. Grönroos, K. M. Irjala, R. K. Huupponen, H. Scheinin, J. Forsström and JJF. A medication database - A tool for detecting drug interactions in hospital. *Eur J Clin Pharmacol*. 1997;53(1):13–17.
8. Andersson ML, Böttiger Y, Lindh JD, Wettermark B, Eiermann B. Impact of the drug-drug interaction database SFINX on prevalence of potentially serious drug-drug interactions in primary health care. *Eur J Clin Pharmacol*. 2013;69, no. 3,:565–571.
9. Poon EG, Keohane CA, Yoon CS, et al. Effect of bar-code technology on the safety of medication administration. *Obstet Gynecol Surv*. 2010;65(10):629-630. doi:10.1097/OGX.0b013e3182021fe9
10. Delgado Silveira E, Soler Vigil M, Pérez Menéndez-Conde C, Delgado Téllez de Cepeda L, Bermejo Viñedo T. Prescription errors after the implementation of an electronic prescribing system. *Farm Hosp*. 2007;31(4):223-230. doi:10.1016/S1130-6343(07)75378-3
11. Çelik N, Şanlıer N. Besin-İlaç Etkileşimlerine Güncel Bakış: İçecekler. *ERÜ Sağlık Bilim Fakültesi Derg*. 2014;2(1):94-101.
12. Bayraktar Ekincioğlu A. Besin ve Besin Ögesi ile İlaç Etkileşimleri. *Beslenme ve Diyet Derg*. 2015;42(2):154-159.
13. Öztürk E, Köse İ, Elmas Ö. Effect of Closed Loop Medication Administration on Drug Returns in Inpatient Facilities. *Med Res Arch*. 2020;8(12).
14. Boullata JI, Hudson LM. Drug-Nutrient Interactions: A Broad View with Implications for Practice. *J Acad Nutr Diet*. 2012;112(4):506-517. doi:10.1016/j.jada.2011.09.002
15. Çetin F. Bağışıklık Sistemi Desteklerinin Besin-İlaç Etkileşimi. *İstanbul Sabahattin Zaim Üniversitesi Fen Bilim Enstitüsü Derg*. 2020;2 (1):14-19. https://dergipark.org.tr/tr/pub/izufbed.
16. Ede, G, Unal RN. Physiological and Pharmacokinetic Alterations and Drug-Nutrient Interactions During Pregnancy. *Istanbul Med J*. 2017;18(3):120-127. doi:10.5152/imj.2017.04875
17. Alphan E, Baş M, Baysal A, Merdol TK, G. K, Pekcan G. *Hastalıklarda Beslenme Tedavisi*.; 2013.
18. Leape LL, Brennan TA, Laird N, et al. The nature of adverse events in hospitalized patients Results of the Harvard Medical Practice Study II. *N Engl J Med*. 1991:7;324(6):377-84. doi:doi: 10.1056/NEJM199102073240605.
19. Aktay G, Hancı H, Balseven A. İlaç

Etkileşimleri ve Hekim Sorumluluğu. *TBB Sürekli Tıp Derg*. 2003;cilt 12 sa:264. xx.
20. Khuda F, Ovais M, Khan A, et al. Drug-food interactions of commonly available juices of Pakistan. *Pak J Pharm Sci*. 2019;32(5):2189-2196.
21. Atik ND, Taşçı A, Orakçı ME, Eyüpoğlu M, Evginer S. Türkiye Diyetisyenler Derneği Üyelerinin Çalışma Ortamlarındaki İş Sağlığı ve Güvenliği Koşulları. 2016;44(1):18-23.
22. Vadamecum.
23. UptoDate. 2020. https://www.uptodate.com/home.
24. Qliktech. Qlikview. https://www.bitechnology.com/. Published 2020.
25. Garg AX, Adhikari NKJ, McDonald H, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: A systematic review. *J Am Med Assoc*. 2005;293(10):1223-1238. doi:10.1001/jama.293.10.1223
26. Čufar A, Droljc A, Orel A. Electronic medication ordering with integrated drug database and clinical decision support system. *Stud Health Technol Inform*. 2012;180(September):693-697. doi:10.3233/978-1-61499-101-4-693
27. Özgür F, Onan Ö. Greyfurt'un İlaçlar ile etkileşimi. *Bilkent Üniversitesi*. http://bilheal.bilkent.edu.tr/aykonu/greyfurt.htm.
28. Kurtoglu Celik G, Pamukcu Gunaydın G, Ozgur Dogan N, Mahmut Dellul M, Sahin Kavaklı H. Pomegranate Juice and Warfarin Interaction: A Case Report. *J Acad Emerg Med Case Reports*. 2014;(1):66-68. doi:10.5152/jaemcr.2014.33255
29. Lasswell AB, DeForge BR, Sobal J, Muncie HL, Michocki. Family medicine residents' knowledge and attitudes about drug-nutrient interactions. *1995*.:137-143. doi:https://doi.org/10.1080/07315724.1995.10718485

