Comparing potential drug-drug interactions in veterinary medications using two electronic databases

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Abstract

Background: One of the most common global health issues in humans and animals is drug-drug interactions (DDIs). This issue increases the risks associated with healthcare in both human and veterinary medicine, as animals live long lives and receive many medicines to treat their illnesses. Currently, many electronic databases are being used as tools for potential DDI prediction, for example, Micromedex and Drugs.com. The purpose of this study was to examine the different abilities for the identification of potential DDIs in veterinary medicines by Micromedex and Drugs.com.

Results: A list of 140 drugs, mainly used for the treatment of disease in animal hospitals, was complied, but the Micromedex and Drugs.com databases could recognise only 96 of these drugs. After inputting the recognised drug list into the databases, Micromedex showed 429 pairs of potential DDIs, whilst Drugs.com showed 842 pairs of potential DDIs. The analysis comparing results between the two databases showed 139 pairs (12.28%) with the same severity and 993 pairs (87.72%) with different severities. Major mechanisms of contraindicated and major potential DDIs were cytochrome P450 induction-inhibition and QT interval prolongation.

Conclusion: Although Micromedex had a lower sensitivity to identify potential DDIs than Drugs.com, Micromedex provided more informative documentation. Veterinary pharmacists should evaluate potential DDIs from several databases and communicate with both the veterinarian and animal owner to ensure an appropriate drug prescription.

Background

Multiple-drug prescriptions for the treatment of diseases and complications usually occurs in humans and animals [1, 2]. One category of adverse drug reactions (ADRs) is defined as drug-drug interactions (DDIs), in which one drug interferes with another. In particular, healthcare providers combine drugs for synergistic action and therapeutic benefit, but toxicity or adverse events may also be possible [3]. DDIs can lead to drug toxicity or decreased therapeutic effect, resulting in increase of morbidity and mortality [4–6]. The degree of severity of DDIs is categorised as follows: contraindicated, major, moderate, minor and none [7, 8]. A serious concern is focusing on the contraindicated and major severities when dispensing drugs to patients as well as animals. Recently, attention has shifted to developing online databases for detecting potential DDIs. Online DDI databases have two major types: open-access resources and subscription databases [9–11]. In general, patients usually select open-access databases, for example, Drugs.com, to access potential DDI identification. Conversely, healthcare providers prefer using a subscription database to identify potential DDIs, for example, Micromedex. Interestingly, these two databases have different features [12] and show different results in identifying potential DDIs between the prescribed drugs for oral cancer treatment [13]. Also, in veterinary medicine as well as human medicine, multidrug therapy is commonly used for the treatment of animals [14]. However, few studies focus on the competency of databases to detect potential DDIs for the management of complicated diseases in animals, for example, cardiovascular diseases, urinary diseases, metabolic diseases, skin

diseases and cancers. These diseases require multiple drug use and might result in DDIs in sick animals. This study aimed to investigate the differences in performance of DDI databases for identifying potential DDIs with complicated disease treatments used in animals.

Results

From the 96 drugs used in this study, 1132 unduplicated pairs were found by the selected databases as potential DDIs. Micromedex identified 429 pairs of potential DDIs and Drugs.com identified 842 pairs of potential DDIs. Table 1 exhibits the classification of severity for the 429 pairs identified by Micromedex as contraindicated in 18 pairs, major in 206 pairs, moderate in 143 pairs and minor in 62 pairs. Meanwhile, Drugs.com classified 842 pairs of potential DDIs as 165 pairs in major degree, 561 pairs in moderate degree and 116 pairs in minor degree. Fig. 1 demonstrates the documentation rating in each severity degree of potential DDIs identified by Micromedex, for which the summation of excellent and good scientific evidence was 63.87% (274/429).

Table 1 Collation result of the potential DDIs between the two databases.

Severity levels	Micromedex n (%)	Drugs.com n (%)
Contraindicated	18 (4.20)	N/A
Major	206 (48.02)	165 (19.59)
Moderate	143 (33.33)	561 (66.63)
Minor	62 (14.45)	116 (13.78)
Total	429 (100.00)	842 (100.00)

N/A, not available

After comparing all of the potential DDI results analysed by the two databases, 139 pairs (12.28%) showed the same severity, whilst 993 pairs (87.72%) of results showed a difference in severity. From all of the results, contraindications and major DDIs identified by Micromedex and major DDIs reported by Drugs.com were selected for determination of the type of mechanism of each potential DDI report, as shown in Table 2. Among the 86 pairs of significant potential DDIs, 15 pairs were at the contraindication degree reported by Micromedex and classified at the major degree by Drugs.com. The remaining 71 pairs were reported at the major degree by both databases.

Table 2 The significant drug pairs in potential DDIs examined by the two databases.

Micromedex	Drugs.com	List of drugs paired	PK-PD	Mechanism details
Contraindication	Major	1. Amiodarone—Dronedarone	PD	Additive QT-interval prolongation
				CYP3A4 inhibition by Ketoconazole
			PK	Additive QT-interval prolongation
				CYP3A4 inhibition by Cyclosporine
		1. Amiodarone—Ketoconazole	PD	CYP3A4 inhibition by Erythromycin
				Additive QT-interval prolongation
		2. Ciprofloxacin—Dronedarone	PK	CYP3A4 inhibition by Itraconazole
				CYP3A4 inhibition by Ketoconazole
		3. Cyclosporine—Dronedarone	PK	Additive QT-interval prolongation
				Additive QT-interval prolongation
		4. Dronedarone—Erythromycin	PD	CYP3A4 inhibition by Itraconazole
				CYP3A4 inhibition by Ketoconazole
		5. Dronedarone—Flecainide	PK	CYP3A4 inhibition by Itraconazole
				CYP3A4 inhibition by Ketoconazole
		6. Dronedarone—Itraconazole	PK	CYP induction by Rifampin
		7. Dronedarone—Ketoconazole	PD	
		8. Dronedarone—Procainamide	PD	
		9. Dronedarone—Sotalol	PK	
		10. Felodipine—Itraconazole	PK	
		11. Felodipine—Ketoconazole	PK	
		12. Itraconazole—Nisoldipine	PK	
		13. Ketoconazole—Nisoldipine	PK	
		14. Praziquantel—Rifampin		
Major	Major	1. Amikacin—Furosemide	PD	Additive or synergistic toxicity
				Decreased clearance of Theophylline by Ciprofloxacin
		2. Aminophylline—Ciprofloxacin	PK	Decreased hepatic metabolism
				Additive effects on QT interval
				P-glycoprotein inhibition by Amiodarone
		1. Aminophylline—Mexiletine	PK	Additive effects on QT prolongation, CYP3A4 inhibition by Erythromycin
			PD	Antiarrhythmic inhibition by Amiodarone, CYP2D6 inhibition by Amiodarone
		2. Amiodarone—Ciprofloxacin	PK	CYP3A4 inhibition by Itraconazole Antiarrhythmic inhibition by Amiodarone
				CYP induction by Rifampin
		3. Amiodarone—Digoxin	PD, PK	Additive effects on refractory potential
				CYP3A4 inhibition by Verapamil
				CYP3A4 inhibition by Diltiazem

		CYP induction by Rifampin
1. Amiodarone—Erythromycin	PD, PK	Additive cardiovascular effects, decreased metabolism of some beta-blockers by Verapamil Additive cardiovascular effects, decreased metabolism of some beta-blockers by Diltiazem Increased potassium retention secondary to lowered aldosterone levels
1. Amiodarone—Flecainide	PK PD	Additive effects of hyperkalemia Additive cardiovascular effects, decreased metabolism of some beta-blockers by Verapamil Additive cardiovascular effects, decreased metabolism of some beta-blockers by Diltiazem An additive effect of risk for tendon rupture
1. Amiodarone—Itraconazole	PK	Additive effects on the QT interval Additive effects on the QT interval
2. Amiodarone—Procainamide	PD PK	Decreased clearance of Theophylline, CYP1A2 inhibition by Ciprofloxacin CYP3A4 inhibition by Itraconazole
1. Amiodarone—Rifampin	PK PK	Cyclosporine metabolism induction by Rifabutin Increased Cyclosporine clearance and decreased systemic bioavailability by Rifampin
2. Amiodarone—Sotalol	PK PD,	P-glycoprotein inhibition by Dronedarone Digoxin metabolism and clearance inhibition by Itraconazole
3. Amiodarone—Verapamil	PK	Increased potassium retention secondary to lowered aldosterone levels Additive effects of hyperkalemia
4. Amiodarone—Diltiazem		CYP3A4 inhibition by Erythromycin and Ketoconazole
5. Amlodipine—Rifampin	PD, PK	CYP3A4 inhibition by Erythromycin Additive effects on QT prolongation
6. Atenolol—Verapamil		CYP3A4 inhibition by Erythromycin CYP3A-mediated inhibition by Diltiazem Additive cardiovascular effects, decreased metabolism of some beta-blockers by Verapamil
1. Atenolol—Diltiazem	PD	Additive cardiovascular effects, decreased metabolism of some beta-blockers by Diltiazem Additive effects on QT prolongation Additive effects on refractory potential
1. Benazepril—Spironolactone	PD PD, PK	CYP3A-mediated inhibition by Itraconazole CYP3A-mediated inhibition by Ketoconazole Additive or synergistic toxicity Additive or synergistic toxicity Additive or synergistic toxicity Additive or synergistic toxicity
1. Benazepril—Trimethoprim	PD, PK	CYP3A4 inhibition by Itraconazole CYP3A4 induction by Rifabutin, CYP3A4 inhibition by Itraconazole CYP3A-mediated induction by Rifampin CYP3A4 inhibition by Itraconazole
2. Carvedilol—Verapamil		Additive QT-interval prolongation CYP3A-mediated inhibition by Ketoconazole, CYP3A-mediated induction by Rifabutin

	PD	CYP3A-mediated induction by Rifampin
		CYP3A4 induction by Rifapentine
	PD	Additive effects on the QT interval
1. Carvedilol—Diltiazem	PD	Additive cardiovascular effects, decreased metabolism of some beta-blockers by Verapamil
	PK	Additive cardiovascular effects, decreased metabolism of some beta-blockers by Diltiazem
		Decreased hepatic metabolism, CYP1A2 inhibition by Mexiletine
		CYP3A4 induction by Phenobarbital
1. Ciprofloxacin—Prednisolone	PK	CYP3A4 induction by Phenytoin
		CYP3A4 induction by Rifabutin
2. Ciprofloxacin—Procainamide	PK	CYP3A4 induction by Rifampin
		CYP3A4 induction by Rifapentine
		Additive effects on refractory potential
3. Ciprofloxacin—Sotalol	PK, PD	Increased potassium retention secondary to lowered aldosterone levels
4. Ciprofloxacin—Theophylline		Additive effects of hyperkalemia
		CYP3A-mediated inhibition by Itraconazole
		CYP3A-mediated inhibition by Ketoconazole
	PK	Additive cardiovascular effects, decreased metabolism of some beta-blockers by Verapamil
1. Cyclosporine—Itraconazole		Additive cardiovascular effects, decreased metabolism of some beta-blockers by Diltiazem
2. Cyclosporine—Rifabutin	PK	Additive effects of hyperkalemia
	PD	
1. Cyclosporine—Rifampin		
	PD	
	PK	
1. Digoxin—Dronedarone		
	PK	
	PD	
1. Digoxin—Itraconazole		
	PK	
	PK	
1. Enalapril—Spironolactone	PD, PK	
1. Enalapril—Trimethoprim	PD, PK	

2. Erythromycin—Ketoconazole	
1. Erythromycin—Procainamide	PD
2. Erythromycin—Sotalol	PD
3. Erythromycin—Verapamil	PK
4. Erythromycin—Diltiazem	PK
5. Esmolol—Verapamil	PD
	PD
1. Esmolol—Diltiazem	PD
	PD
	PK
1. Flecainide—Procainamide	PK
2. Flecainide—Sotalol	
3. Fluticasone—Itraconazole	PK
	PK
1. Fluticasone—Ketoconazole	PD
	PK
1. Furosemide—Gentamicin	
2. Furosemide—Kanamycin	PK
3. Furosemide—Streptomycin	PK
4. Furosemide—Tobramycin	PD
5. Itraconazole—Nifedipine	PD, PK
6. Itraconazole—Rifabutin	
	PD, PK

1. Itraconazole—Rifampin	
2. Itraconazole—Sildenafil	PK
3. Ketoconazole—Procainamide	
4. Ketoconazole—Rifabutin	PK
	PK
	PK
1. Ketoconazole—Rifampin	PK
2. Ketoconazole—Rifapentine	PK
3. Ketoconazole—Sotalol	PD
4. Metoprolol—Verapamil	PD
	PD
1. Metoprolol—Diltiazem	PK
	PK
1. Mexiletine—Theophylline	PD, PK
1. Nifedipine—Phenobarbital	PD, PK
2. Nifedipine—Phenytoin	
3. Nifedipine—Rifabutin	PD
4. Nifedipine—Rifampin	
5. Nifedipine—Rifapentine	
6. Procainamide—Sotalol	

7. Ramipril—Spironolactone

1. Ramipril—Trimethoprim
2. Salmeterol—Itraconazole

1. Salmeterol—Ketoconazole

1. Sotalol—Verapamil

1. Sotalol—Diltiazem

1. Spironolactone—Trimethoprim

In terms of mechanism, 51% (44/86) were pharmacokinetics (PK)-based, 34% (29/86) were pharmacodynamics (PD)-based and 15% (13/86) were PK-PD-based. The majority of PK-based DDIs involved cytochrome P450 (CYP) induction and inhibition, whilst PD-based DDIs caused QT prolongation and potassium retention. We also found some conflict between the results of the two databases, in which one database reported potential DDIs as major but another one reported them as minor or not DDIs. For the dissimilar results as shown in Table 3, 32 pairs were identified by Micromedex as major DDIs but only minor or not DDIs by Drugs.com. Conversely, 53 pairs were specified as major DDIs by Drugs.com whilst Micromedex identified these as not DDIs.

Table 3 Different results between the two databases in the identification of the potential DDIs

Micromedex	Drugs.com	List of drugs paired
Major	Minor	1. Amiodarone—Sulfamethoxazole 2. Digoxin—Gentamicin 3. Digoxin—Spironolactone 4. Digoxin—Trimethoprim 5. Erythromycin—Sulfamethoxazole 6. Flecainide—Trimethoprim 7. Lidocaine—Phenytoin 8. Procainamide—Sulfamethoxazole 9. Sotalol—Sulfamethoxazole
Major	None	1. Amiodarone—Trimethoprim 2. Amlodipine—Digoxin 3. Amoxicillin—Chlortetracycline 4. Amoxicillin/Clavulinate—Chlortetracycline 5. Ampicillin—Chlortetracycline 6. Chlortetracycline—Methicillin 7. Chlortetracycline—Nafcillin 8. Chlortetracycline—Oxacillin 9. Chlortetracycline—Penicillin G 10. Chlortetracycline—Penicillin V 11. Digoxin—Felodipine 12. Digoxin—Isradipine 13. Digoxin—Meloxicam 14. Digoxin—Nicardipine 15. Erythromycin—Trimethoprim 16. Flecainide—Lidocaine 17. Flecainide—Trimethoprim 18. Isradipine—Procainamide 19. Isradipine—Sulfamethoxazole 20. Isradipine—Trimethoprim 21. Itraconazole—Sotalol 22. Mexiletine—Sotalol 23. Sotalol—Trimethoprim
None	Major	1. Albuterol—Carvedilol 2. Amikacin—Polymyxin B

3. Aminophylline—Carvedilol
4. Amiodarone—Furosemide
5. Amiodarone—Nafcillin
6. Amiodarone—Phenobarbital
7. Amiodarone—Rifabutin
8. Amiodarone—Terbutaline
9. Amlodipine—Rifabutin
10. Atenolol—Aminophylline
11. Atenolol—Theophylline
12. Diltiazem—Flecainide
13. Diltiazem—Itraconazole
14. Diltiazem—Rifabutin
15. Erythromycin—Itraconazole
16. Erythromycin—Sildenafil
17. Esmolol—Aminophylline
18. Felodipine—Rifabutin
19. Gentamicin—Polymyxin B
20. Isradipine—Phenobarbital
21. Isradipine—Rifabutin
22. Itraconazole—Amlodipine
23. Itraconazole—Isradipine
24. Itraconazole—Nicardipine
25. Itraconazole—Rifapentine
26. Kanamycin—Polymyxin B
27. Metoprolol—Aminophylline
28. Metoprolol—Theophylline
29. Nicardipine—Phenobarbital
30. Nicardipine—Rifabutin
31. Phenobarbital—Amlodipine
32. Phenobarbital—Nisoldipine
33. Phenytoin—Felodipine
34. Phenytoin—Isradipine
35. Phenytoin—Nicardipine
36. Phenytoin—Amlodipine
37. Procainamide—Terbutaline
38. Rifabutin—Nisoldipine

39. Rifampin—Cefamandole
40. Rifampin—Felodipine
41. Rifampin—Nicardipine
42. Salmeterol—Carvedilol
43. Sotalol—Albuterol
44. Sotalol—Aminophylline
45. Sotalol—Salmeterol
46. Sotalol—Terbutaline
47. Streptomycin—Polymyxin B
48. Terbutaline—Carvedilol
49. Theophylline—Carvedilol
50. Theophylline—Esmolol
51. Theophylline—Sotalol
52. Tobramycin—Polymyxin B
53. Verapamil—Itraconazole

Discussion

The two databases used in our study could recognise animal medicines less frequently than human medicines. This may be because the databases do not include complete information about animal medicines in their DDI databases. However, Drugs.com included a list of veterinary products that covered many animal species and provided useful information, for example, dosage, administration, precautions and adverse reactions. Therefore, veterinary pharmacists should use this drug database for searching for drug information and as a source for reference documents. The potential DDI results from the drug lists were different for the two electronic databases. In this study, the results from Drugs.com exhibited a higher number of potential DDIs than Micromedex by nearly 2.0 times. This result was correlated with Lauren et al., who found that Drugs.com had higher sensitivity than Micromedex for screening DDIs in oral cancer treatment [13]. Suriyapakorn et al. compared the capability of the databases to identify potential DDIs with metabolic syndrome medications and also found that Drugs.com provided more sensitivity than the other database [15]. The reason for the high sensitivity of Drugs.com in identifying DDIs may be caused by using databases from many providers to analyse data that is contained in Micromedex. We compared the result from Micromedex between the drug list used for metabolic syndrome in human and animal diseases in identity contraindicated and major potential DDIs. The drug list for animal disease treatment identified more pairs of contraindicated and major potential DDIs; the reason might be that the drugs used in animals included many drugs related to antiarrhythmic agents, antimicrobials and antihypertensive drugs, which often show a high incidence of potential DDI when prescribed with other drugs [16–18]. Veterinary pharmacists should realise when prescribing these drug groups to avoid the severe adverse reactions.

The combination of drugs prescribed to treat canine atopic dermatitis were identified as a potential DDIs; for instance, a co-prescription of ketoconazole with cyclosporine has been suggested, which could reduce the therapeutic cost and is convenient to use. This combination appears to provide greater clinical benefits for the treatment than disadvantages. Nevertheless, an excessive number of alerts of potential DDI lacking supporting information could cause wearying to healthcare providers as well as animal owners. Many healthcare providers dislike using drug interaction databases [19] for several reasons, including alert fatigue [20–21], workflow disturbance [22] and believing that there is no clinical significance related to most DDI alerts [23]. Ideally, an applicable drug interaction database should have both high sensitivity in identifying significant interactions and high specificity in excluding insignificant interactions. As a result, healthcare providers should be sure to use more than one DDI reference for reaching the best final answer when identifying potential DDIs [24]. Apart from using several DDI databases, healthcare providers should share their decision-making with animal owners regarding any significant potential DDI pairs, to preclude animals from adverse events and minimise liability.

In multiple-drug prescriptions, drug dosages usually have a relationship with drug interactions. For example, giving high doses of some drugs may cause interactions, but if they are used at lower doses, the possibility of a DDI may decrease. Ideally, the DDI database should be able to overlook an interaction if the given drugs are at doses that will not likely develop into a DDI [25–26], which the two databases in this study were not able to do. Therefore, the input of dosage should be added to databases, so healthcare providers can select the dose of drugs under consideration. Interestingly, Micromedex and Drugs.com provide detailed information differently. Micromedex adds more information on allergy interaction, alcohol interaction, lab interaction, tobacco interaction, pregnancy interaction and lactation interaction; Drugs.com provides more information only on food interactions and presents results into two categories: consumer and professional. The diversity of information from these two databases gives many benefits to increase the confidence of healthcare providers when many health conditions are discussed with their clients.

For determination of the mechanisms of potential DDIs in contraindicated and major severity levels identified by the two databases, PK-based was the main mechanism of DDI, followed by PD-based and PK-PD-based. The PK-based DDI causes a change of drug concentration in plasma or at the targeted organ by altering the absorption, distribution, metabolism and elimination. In this study, CYP enzyme inhibition was the main result of PK-based DDI, which leads to the accumulation of co-administered drugs, for example, ciprofloxacin inhibits CYP1A2 activity and decreases the clearance of theophylline, resulting in fatal adverse drug reaction via drug toxicity. PD-based DDI is caused by one drug interfering with another drug at the target site. The main result of PD-based DDI in our study was QT prolongation, which may lead to irregular heart rhythm and sudden death, for example, co-administration of erythromycin with sotalol may result in an additive QT prolongation. As a result, healthcare providers should truly understand these DDI mechanisms to prescribe multiple drugs properly.

This study has several important limitations. The most important one is that only two drug databases were used for the evaluation, so future studies should include additional databases of both subscription

and open-access type, such as Lexicomp and Epocrates Free, respectively. Changing of the drug list was also one of our concerns; each year new drugs were developed whilst old drugs disappeared. The drug list used in this study was gathered in the first quarter of 2020, so it might have changed at any time. The updating frequency of databases for their potential DDI reports might affect the results of the analysis. The potential DDI result produced by the updated version of Micromedex and Drugs.com at different time points might give different outcomes from our study, performed in the first quarter of 2020. Additionally, the two databases have no data on several drugs used in animal hospitals, resulting in incomplete potential DDI analysis. Hence, some differences may occur once all drugs are added into the databases. Finally, the results of all probable mechanisms of action in our study referred to humans, which might differ from animals due to dissimilar physiology and drug-metabolising enzyme systems [27]. Therefore, more study of potential DDIs in animals is recommended to improve medical care and decrease the possibility of DDIs as a result of multidrug therapy in animals.

Conclusions

Drug interaction databases showed highly variable performance in assessing the DDIs of veterinary drugs. Open-access resources, such as Drugs.com, could detect more potential DDIs. However, Micromedex, a subscription database, provided more supportive information and special features. The judgement of healthcare providers should be used, with the consent of animal owners, to determine appropriate treatments for animals and avoid potential DDIs by using several databases for the data evaluation.

Materials And Methods

Drug selection

A list of 578 drugs was taken from those used in one animal hospital in Thailand and the VetList database [28], on 9 January 2020. From the total, 140 drugs were selected as frequently prescribed for the treatment of diseases in animal hospitals. Remarkably, Micromedex and Drugs.com could not recognise 44 of these drugs, so those remaining were used for this analysis, as shown in Fig. 2 and Table 4. The unrecognised 44 items were aditroprim, afoxolaner, avoparcin, baquiloprim, carprofen, clomocycline, danofloxacin, demethylchlortetracycline, deracoxib, difloxacin, enrofloxacin, eprinomectin, fipronil, firocoxib, glutathione, ibafloxacin, imidacloprid, imidapril, ivermectin, levosimendan, limecycline, marbofloxacin, methacycline, methoprene, milbemycin oxime, moxidectin, oclacitinib, orbifloxacin, ormetoprim, pimobendan, pirlimycin, pradofloxacin, rolitetracycline, samylin, spiramycin, sulfadimethoxine, sulfadoxine, sulfamethazine, teicoplanin, tepoxalin, tilmicosin, tulathromycin, tylosin and virginiamycin.

Table 4 List of drugs used for the potential DDIs analysis

Drug class	Drug groups	Drug lists
Analgesics	Nonopioid	1. Meloxicam
Anthelminthics	N/A	1. Praziquantel
Antiarrhythmics	Antiarrhythmic agent class I	1. Flecainide 2. Lidocaine 3. Mexiletine 4. Procainamide
	Antiarrhythmic agent class III	1. Amiodarone 2. Dronedarone 3. Sotalol
	Antiarrhythmic agent class IV	1. Diltiazem
	Beta-blockers	1. Atenolol 2. Esmolol 3. Metoprolol
	Cardiac glycoside	1. Digoxin
Antimicrobials	Aminoglycosides	1. Amikacin 2. Gentamycin 3. Kanamycin 4. Streptomycin 5. Tobramycin
	Carbapenems	1. Primaxin
	Cephalosporins	1. Cefamandole 2. Cefotaxime 3. Cephalexin 4. Cephalothin 5. Ceftriaxone
	Chloramphenicols	1. Chloramphenicol
	Fluoroquinolones	1. Ciprofloxacin
	Glycopeptides	1. Vancomycin

	Lincosamides	1. Clindamycin 2. Lincomycin
	Macrolides	1. Erythromycin
	Monobactams	1. Aztreonam
	Penicillinase resistant penicillins	1. Methicillin
	Penicillins	1. Amoxicillin/Clavulinate 2. Amoxicillin 3. Ampicillin 4. Carbenicillin 5. Nafcillin 6. Oxacillin 7. Penicillin G 8. Penicillin V
	Polymyxins	1. Polymyxin B 2. Polymyxin E
	Rifamycins	1. Rifabutin 2. Rifampin 3. Rifapentine
	Sulfonamides	1. Sulfadiazine 2. Sulfamethoxazole
	Tetracyclines	1. Chlortetracycline 2. Doxycycline 3. Minocycline 4. Oxytetracycline
	Trimethoprims	1. Trimethoprim
Anticonvulsants	Barbiturates	1. Phenobarbital
	Hydantoin	1. Phenytoin
	Benzodiazepine	1. Diazepam

	Miscellaneous	1. Gabapentin 2. Pregabalin
Antifungal agents	Azole derivatives	1. Itraconazole
	Imidazole derivatives	1. Ketoconazole 2. Miconazole
Antihistamines	H_1 receptor antagonists	1. Cetirizine 2. Chlorpheniramine
Antihypertensive drugs	Angiotensin-converting enzyme inhibitors	1. Benazepril 2. Enalapril 3. Ramipril
	Beta-blockers	1. Carvedilol
	Calcium channel blockers	1. Amlodipine 2. Felodipine 3. Isradipine 4. Nifedipine 5. Nisoldipine 6. Verapamil 7. Nicardipine
Antitussives	N/A	1. Dextromethorphan
Bronchodilators	Beta-2 receptor agonists	1. Salmeterol 2. Terbutaline 3. Ventolin
	Phosphodiesterase inhibitors	1. Aminophylline 2. Theophylline
Corticosteroids	Systemics	1. Prednisolone
	Topicals	1. Fluticasone
Diuretics	Loop diuretics	1. Furosemide 2. Torsemide
	Potassium-sparing	

		1. Spironolactone
Hormones	Thyroid products	1. Levothyroxine
Herbal products	N/A	1. Aloe vera
Immunosuppressants	Calcineurin Inhibitors	1. Cyclosporine
Mucolytic agents	N/A	1. Acetylcysteine
Expectorants	N/A	1. Guaifenesin
Vasodilating agents	Phosphodiesterase-5 enzyme inhibitors	1. Sildenafil
Miscellaneous	Amino acid supplements	1. Methionine
	Antioxidants	1. Alpha-lipoic acid
	Antiseptics	1. Chlorhexidine
	Liver supplements	1. SAM-E (S-adenosylmethionine)
	Vitamin like substances	1. Coenzyme Q10

N/A, not available

Drug interaction databases selection

The subscription drug interaction database Micromedex (Truven Health Analytics, USA) was selected for the analysis of potential DDI on the basis of local availability through Chulalongkorn University. The open-access drug interaction database Drugs.com (Drugsite Trust, USA) was used because this database is well known and easy to use. The results of DDI from the two databases provided the same information, as follows: severity levels, probable mechanism, clinical management, literature and references. However, Micromedex provided more supportive information about documentation levels and the onset of the interaction.

DDI categorisation

For every selected drug queries posed to the databases, the two drug interaction databases categorised potential DDIs with a few different formats and explanations. Micromedex has five severity categories to identify potential DDIs, as follows: contraindicated, major, moderate, minor and unknown. Drugs.com has no category for contraindicated. Interestingly, only Micromedex categorised the documentation level for the detected potential DDIs, at three levels, as follows: excellent – the interaction has been clearly verified

from controlled studies; good – the interaction is strongly suspected but lacks well-controlled studies; fair – availability of documentation is poor but the interaction is suspected to exist on the basis of pharmacological considerations, or a pharmacologically related drug provides good documentation. All results of the potential DDIs in this study were obtained from searches in the two databases and gathered in January 2020.

List Of Abbreviations

ADR: Adverse drug reaction

CYP: Cytochrome P450

DDI: Drug-drug interaction

PD: Pharmacodynamics

PK: Pharmacokinetics

Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Additional material

Not applicable.

Availability of data and materials

All data are presented in the manuscript.

Competing interests

Each author declares no competing interests.

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Authors' contributions

TB collected, analysed, and interpreted the data and drafted the manuscript.
PK contributed to study design, data analysis, and revising the manuscript.
AK contributed to study design, data analysis, and revising the manuscript.
All authors have read and approved the final version of the manuscript.

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Figures

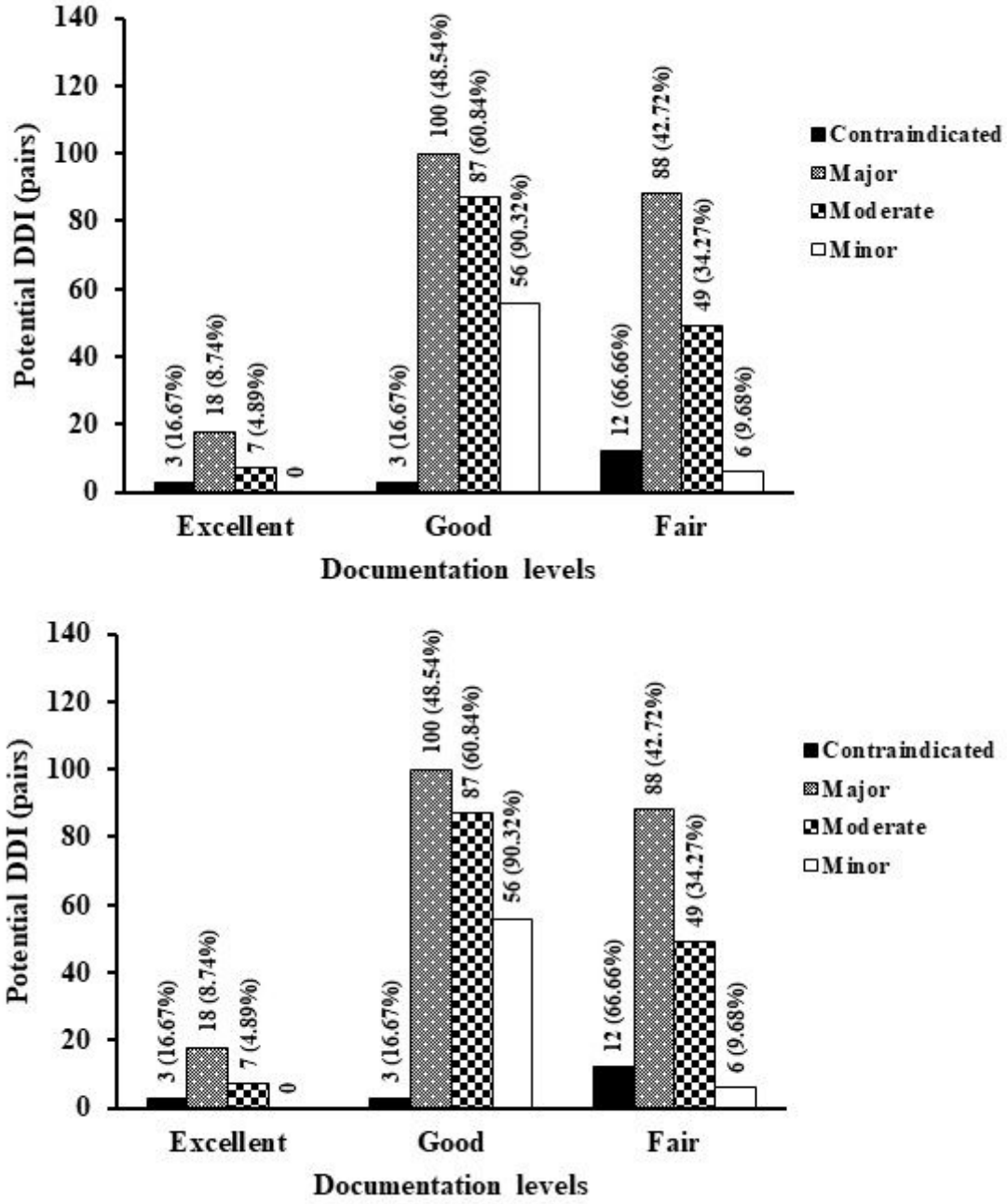

Figure 1

Result of the potential DDIs in each documentation level of Micromedex

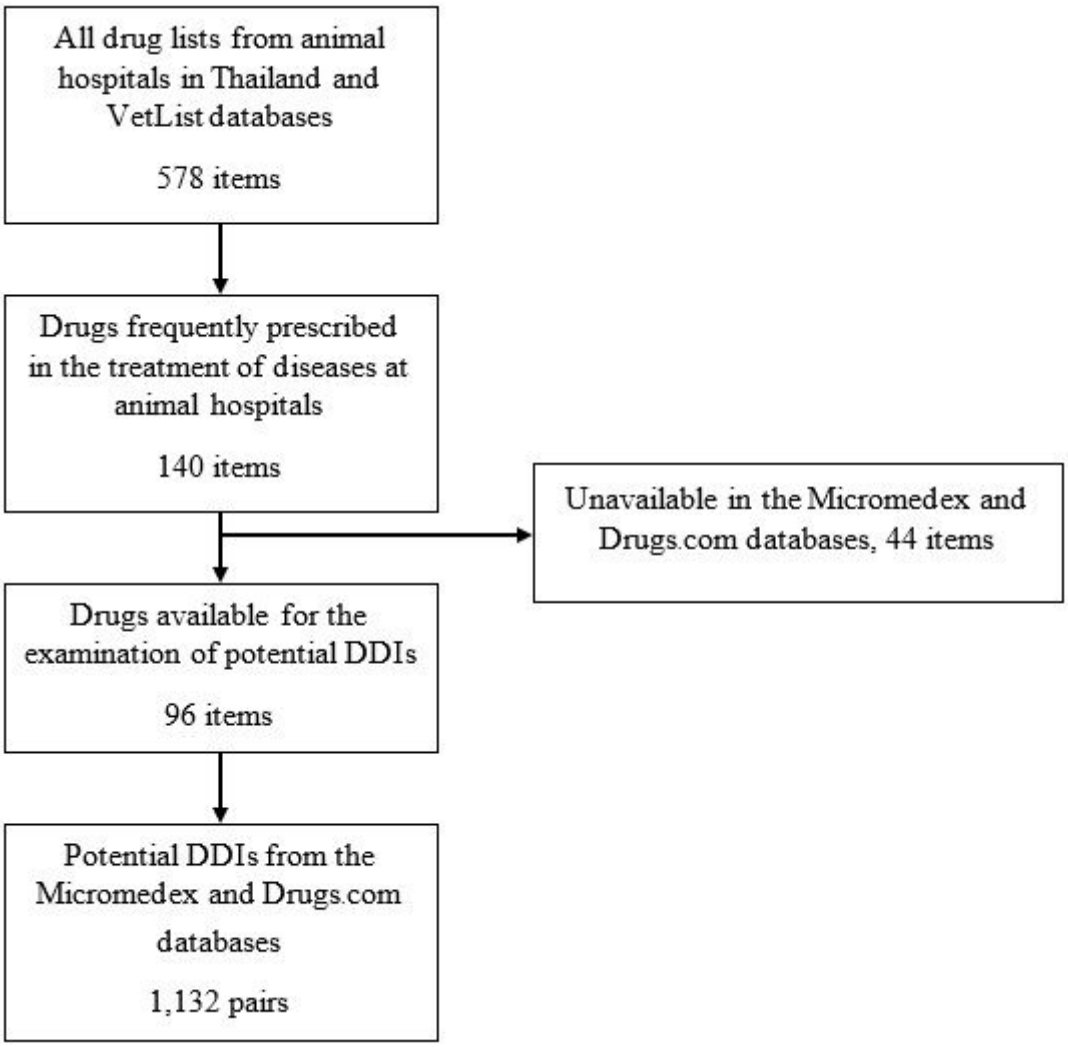

Figure 2

Procedure for drug selection