Pharmacological Review of Drug Interactions

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ABSTRACT

Drug interaction (DI) occurs when the effects of one drug are altered by the presence of another drug, herbal medicine, foods, drink or by some environmental or chemical agents". Any time a drug is administered with another prescription or over the counter drug, herb or food item, there is the risk of interactions which may be potentially dangerous. Drug-drug interaction increases with the number of drugs used concomitantly. The drug whose activity is effected by such interaction is referred to as the "Object drug" while the agent that eventually precipitates such an interaction is referred to as the "Precipitant / Perpetrator drug". It is worthy of note that drug interactions may cause drugs to be less effective, may induce unexpected side effects or rarely even increase the action of a particular drug. Many drug interactions have been found to be harmful. Approximately 3– 26% of adverse reactions related to hospital admissions are due to drug-drug interactions while, global prevalence of potentially inappropriate prescribing ranges from 13–35%.

Up to 11.1% of patients actually experience drug interactions symptoms. An appraisal of drug interactions will help update our knowledge on the possible etiologies, mechanisms of action, adverse effects, clinical effects and desired advancements in therapies for drug interactions as well ways of managing same. Secondly, the systematic knowledge of drug interaction, especially at the level of absorption, elimination, transport and drug metabolism (pharmacokinetic profiles / variables) may help to prevent adverse effects. Predicting pharmacodynamic interactions often demands a deeper understanding of the mechanisms of effect even as Electronic prescribing systems have been found to be helpful in recent times. Also the rising cases of drug interactions in tropical and

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other regions of the world coupled with scarcity of literature in the subject area under study mandates the necessity for this write up, hence we write.

Sources of literature were from PubMed, Science Direct, Scopus and Google Scholar etcetera. The knowledge of drug interaction at level of absorption, elimination, transport and drug metabolism may help prevent adverse effects. Predicting pharmacodynamic interactions often demands a deeper understanding of the mechanisms of action even as electronic prescribing systems may be helpful.

Keywords: Adverse effects, Chemical agent, Drug interaction, Food, Herbal medicine, Object drug, Precipitant drug.

INTRODUCTION

Drug Interaction (DI): "Drug interaction is said to occur when the effects of one drug are changed by the presence of another drug, herbal medicine, food, drink or by some environmental chemical agent" (Baxter L (ed) Stockley's Drug Interactions).

Drug interaction can equally be defined as a change in action or side effects of a drug caused by concomitant administration of a drug with another drug, supplement, food, beverage or food. At any time, a drug is administered with any other prescription drug, over-the-counter (OTC) drug, herb or food item, one is exposed to the risk of drug interactions which may be potentially dangerous. Drug-drug interaction increases with the number of drugs administered concomitantly. The drug whose activity is effected by such interaction is referred to as the "Object Drug" while the agent that eventually precipitates such an interaction is referred to as the "Precipitant / Perpetrator Drug" (Sunisha Kulkarni, Drug Interaction).

It is worthy of note that drug interactions may cause drugs to be less effective, may induce unexpected side effects or increase the action of a particular drug though rarely. Many drug interactions have been found to be harmful. (Drug Interactions / www.pueblo.gsa.gov 3/2004).

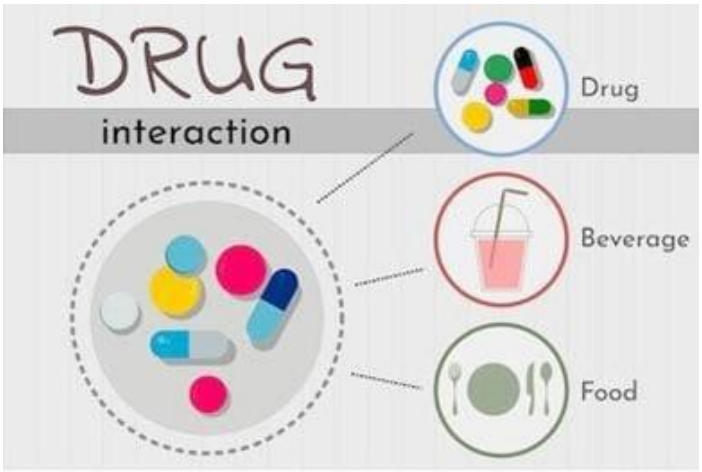
The systematic knowledge of drug interaction, in particular on the level of absorption, elimination, transport and drug metabolism (Pharmacokinetic profiles) may help to prevent adverse effects. Predicting Pharmacodynamic interactions often demands a deeper understanding of the mechanisms of effect / action, while noting that electronic prescribing systems are helpful.

Incidence of Drug Interaction (DI)

Approximately **3–26%** of adverse reactions related to hospital admissions are due to drug-drug interactions while, Global prevalence of potentially inappropriate prescribing ranges from **13– 35%.**

Up to **11.1%** of patients actually experience symptoms from drug interactions (Temi Abimbola, 2022).

FIG. 1. Types of Drug Interactions



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(Fig. 1, Picture Adopted from: (Sunisha Kulkarni, Drug Interaction**)**

Drug Interactions can be:

Undesirable drug interactions mostly or Desirable (beneficial) effects rarely. E.g. enhancement of activity of penicillin when coadministered with probenecid.

Causes of Drug Interactions

Many causes of drug interactions do exist. Namely, one drug may alter / change the known pharmacokinetic profiles or activity of another. Alternatively, drug interactions may result from competition for a single receptor or signaling pathway (Sunisha Kulkarni, Drug Interaction).

Factors Contributing to Drug Interactions May Include:

1. Multiple drug prescription Wrong choice of drug
2. Multiple diseases / illness Wrong route of administration
3. Patients advancing age Errors in taking the drug
4. Multiple drug therapy
5. Poor patient compliance Failing to take account of renal function
6. Multiple pharmacological effects of drug 13. Wrong dosage
7. Transmission errors
8. Drug related factors (Sunisha Kulkarni, Drug Interaction; Cascorbi Ingolf, 2012).

Drug Interactions Most Likely Occur:

i. As a new drug is started

ii. During stoppage of medication

iii. Mechanism of reaction or action of participant drugs often affects the timing

iv. For drugs with long half-life (like Amiodarone) interaction may not be seen immediately

v. Enzyme inducers: maximum effect is noticed 1-3 weeks

vi. Enzyme inhibitors: effects noticed often within 24 hours (Temi Abimbola, 2022).

Types of Drug Interactions:

Different types of drug interactions have been documented form studies. They may include any of the following:

1. Drug-Drug Interactions
2. Drug-Food Interactions
3. Drug-Chemical Interactions
4. Drug-Laboratory Test Interactions
5. Drug-Disease Interactions

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6. Drug Patient Interaction (Sunisha Kulkarni, Drug Interaction; pueblo.gsa.gov 3/2004).

Drug Interactions May Further be Grouped into Three Broad Categories:

1. Drug-drug interactions: This type of drug interaction is said to occur when two or more drugs react with each other. The more the number of drugs co-administered, the more the chances of Drug interaction. This drug-drug interaction may lead to an unexpected side effect.

An example is the mixing a sedative sleeping agent and an antihistamine (anti-allergic agent). The two (2) drugs can interact leading to slowed reaction or actions. In such a situation, driving a car or operating machinery equipment may be very dangerous.

2. Drug-food/beverage interactions: Here drugs may react with foods or A typical example is mixing alcohol with some drugs that may cause tiredness or slowed actions.

3. Drug-condition interactions: This type may occur when an existing medical condition makes certain drugs potentially harmful. A typical example is seen with hypertensive patients on nasal decongestants. Such patients may experience further unwanted reactions (Sunisha Kulkarni, Drug Interaction; pueblo.gsa.gov 3/2004).

Drug Interactions May Equally be Classified into Two (2) Broad Classes:

1. Minor drug Interactions and

2. Major drug Interactions (Temi Abimbola, 2022).

The Net Effect of a Drug-Interaction May be Any of:

1. Generally quantitative–increased or decreased effect.

2. Seldom qualitative–rapid or slower effect.

3. Increased adverse effects (toxicities) or precipitation of newer adverse effects

4. They may equally lead to: Reduced Pharmacological Efficacy (Sunisha Kulkarni, Drug Interaction; Temi Abimbola, 2022).

Mechanisms of Drug Interactions: Two Broad Types

Pharmacokinetics & Pharmacodynamics Mechanisms of DI

PHARMACOKINETIC MECHANISMS OF DRUG INTERACTIONS

Pharmacokinetic drug–drug interactions

Pharmacokinetics is **'what the body does to the drug' or the time course effect of drugs**. These interactions occur when one drug **(the Perpetrator / Precipitant Drug)** alters the concentration of another drug **(the Object Drug)**, often with clinical consequences (Ben D Snyder et al, 2012).

Altered bioavailability

In this mechanism, the amount of the object drug reaching the systemic circulation is affected by a Perpetrator or Precipitant drug. **Following absorption and First-pass metabolism of orally administered drugs, altered Bioavailability may occur.** This is more often **seen with drugs having low oral bioavailability while those with high bioavailability are seldom affected.**

Alendronate and Dabigatran have low oral bioavailability.

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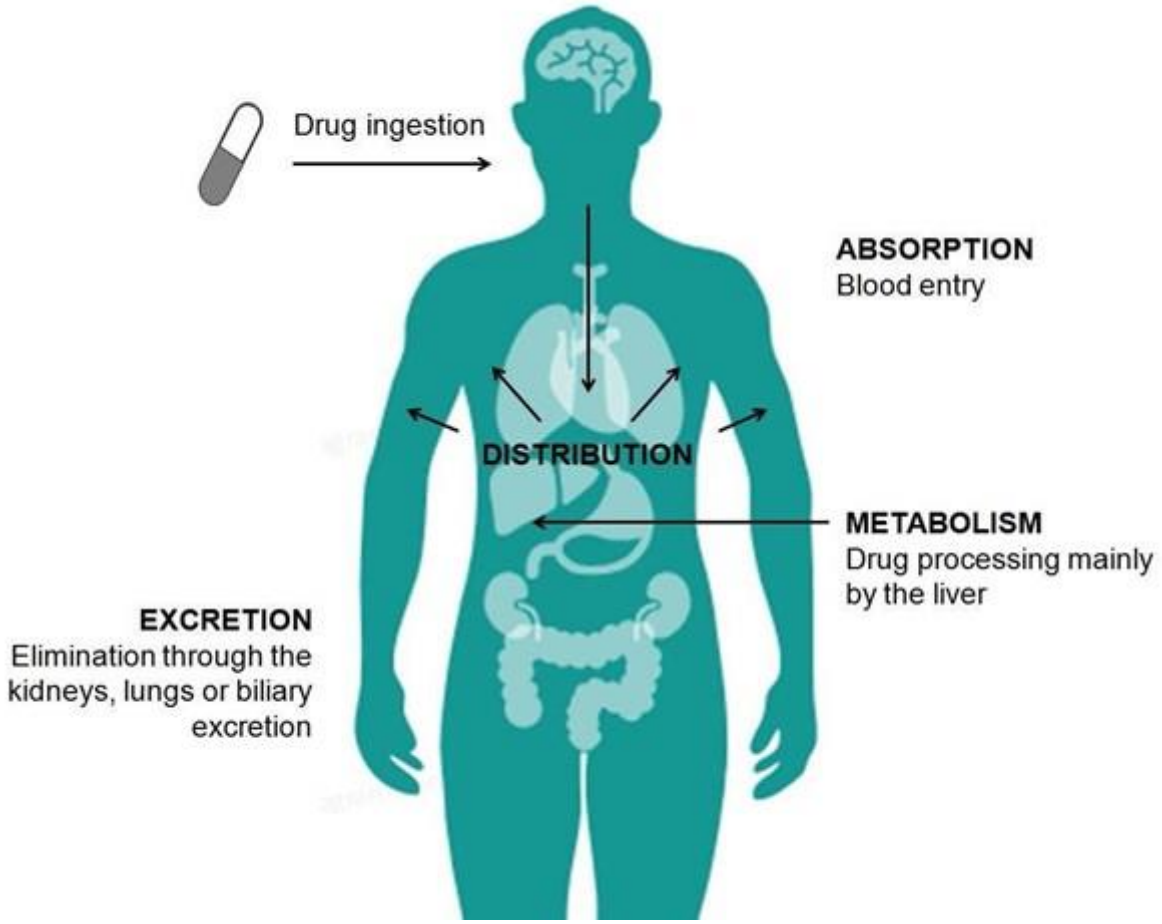
Fig. 2: Mechanism of Drug Interactions: (See Below).



(Fig. 2, Adopted from: Temi Abimbola, 2022. Understanding Drug Interactions for Drug Prescribing Practice).

PHARMACOKINETIC MECHANISMS OF DRUG INTERACTIONS CONT'D

Altered bioavailability Cont'd

The **co-administration of Alendronate with calcium decreases bioavailability** and can result in no Alendronate being absorbed in some instances (low plasma concentration). On the other hand, the co-administration of Dabigatran with Verapamil **increases bioavailability,** hence an increased plasma concentration ensures and may result in an increased risk of bleeding (Ben D Snyder et al, 2012).

Altered clearance

Altered clearance is said to occur when the **excretion or metabolism** of an **Object drug** is affected by a **Perpetrator drug.** Very highly vulnerable are some **Object drugs** having narrow therapeutic index (see Table 1) since modest changes in concentration may be clinically significant. Perpetrator drugs known to strongly affect drug metabolism are more likely to cause large concentration changes and hence clinical consequences. Clinically, the recognition of these potential perpetrators of pharmacokinetic drug–drug interactions remain very important (Ben D Snyder, 2012; Polasek et al, 2011).

Metabolism

The most important causes of unexpected drug interactions are seen with **"drug metabolism".** Changes in drug clearance or oral bioavailability brings about these types of drug interactions. ***In drug metabolism, several enzyme families are involved, though the cytochrome P450 (CYP 450) enzyme family remains the most important.***

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The inhibition of a Cytochrome P450 enzyme increases the concentration of some drugs by decreasing their metabolism. A typical example of this is **Clarithromycin** which is a **strong inhibitor of CYP3A-catalysed Simvastatin metabolism,** thus increasing the risk of **myopathy** (Jacobson TA, 2004; Ben D Snyder et al, 2012).

Conversely **the induction of a Cytochrome P 450 enzyme** is known to **decrease the concentration** of some drugs by **increasing their metabolism.** An example of this type is, Carbamazepine which is **a strong inducer of CYP3A that increases the metabolism of the combined oral contraceptive,** thus **increasing the risk of unwanted pregnancy** (Sabers A, 2008; Ben D Snyder et al, 2012).

It is known that the drug inhibition of **CYP 450 enzyme may also be** used therapeutically. **A typical example is Ritonavir, which is a strong inhibitor of CYP3A. Rotinavir is known to reduce the metabolism of other protease inhibitors thus increasing their effectiveness in treating HIV.** ***This is the so called 'ritonavir-boosted' regimens*** (Walmsly A, 2002; Ben D Snyder et al, 2012).

Excretion

Certain drugs are excreted from the body unchanged in the active form. The excretion is usually in the faeces through the biliary tract or in the urine. *The changes in renal drug clearance may occur due to effects on urine pH or renal tubular function. An example is seen when probenecid reduces the renal clearance of anionic drugs such as Penicillin and Methotrexate* (Ben D Snyder et al, 2012).

Prodrugs:

The conversion of some drugs to their active forms rely on cytochrome P450 enzymes. Prodrugs are particularly vulnerable to changes in metabolism since this is usually dependent on a single enzyme pathway. If the conversion of prodrugs to active drug is inhibited, this may lead to inadequate concentrations of the active drug and hence therapeutic failure may ensure. *An example of this may be seen when Tamoxifen is metabolized by CYP2D6 to its active form Endoxifen.* Also the concomitant therapy with the strong CYP2D6 inhibitor, Paroxetine has been associated with increased mortality in breast cancer (Kelly CM et al 2010; Ben D Snyder et al, 2012).

PHARMACODYNAMICS MECHANISMS OF DRUG INTERACTIONS (DI)

Pharmacodynamic Drug Interactions:

Pharmacodynamic action is **'what the drug does to the body' or the various modes of action of the drug** under use (Leo Clinton, 2021).

The change in an organism's response upon administration of a drug is an important factor in pharmacodynamic interactions. The well-founded suspicion exists that there are more unknown interactions than the known.

The Pharmacodynamic (pharmacological) effects of one drug may be changed by the presence of another drug at its site of action OR-

Indirectly, when interference with physiological mechanisms are involved: these interactions are less difficult to classify neatly than those of a pharmacokinetic type of interactions (Temi Abimbola, 2022).

Pharmacodynamic drug interaction could either be:

a. Antagonistic e.g: When Drugs can compete for the same receptor e.g., **Beta blockers- Propranolol and Beta Agonist- Salbutamol** (antagonistic). Other examples will include: **Antagonistic:**

1. Temazepam and caffeine
2. Warfarin and vitamin K

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3. Beta-blockers and salbutamol OR-

b. Additive e.g: During Aspirin and Warfarin increased Anticoagulation, Salbutamol and Diuretics increased risk of Hypokalaemia.

Other examples will include: **Additive:**

1. Alcohol and CNS depressants
2. Anticholinergics and tricyclic antidepressants
3. Beta blockers and calcium channel blockers (Temi Abimbola, 2022).

Pharmacodynamic interactions can occur on:

1. Pharmacological receptors:

Receptor interactions are the most easily defined as well as the most common. From a pharmacodynamics point of view, drugs can be considered to be:

a. *Homodynamic*, if they act on the same receptor. **The two drugs in turn can be pure agonists, partial agonists or antagonists, and**

b. *Heterodynamic competitors,* if they act on different / distinct receptors.

2. Antagonic physiological systems: If we consider a drug, **A** that acts on a certain body organ. The effect drug **A** will increase with increasing concentrations of physiological substance, **S** in the organism. Also consider a drug, **B** that acts on another organ, which increases the amount of substance, **S**. If both drugs **A** & **B** are taken simultaneously, it is possible that drug, **A** could cause an adverse reaction in the organism as its effect will be indirectly increased by the action of drug, **B**. The typical example of this interaction is found in the concomitant use of **Digoxin** and The former **(Digoxin)** acts on cardiac fibres and its effect is increased if there are low levels of potassium (K) in blood plasma. **Furosemide** is a diuretic that lowers arterial tension but favours the loss of K^+ **(K^+ wasting diuretic).** This could lead to hypokalemia, which could increase the toxicity of digoxin. This effect is unlikely if **Spironolactone**, a PotassiumSparing Diuretic **(K^+ sparing diuretic)** is concomitantly used with Digoxin.

3. Signal transduction mechanisms: These are molecular mechanisms or processes that commence after the interaction of the drug with the receptor. For example, it is known that hypoglycaemia in an organism produces a release of catecholamines, which in turn triggers compensatory mechanisms thereby increasing blood glucose levels. The release of catecholamines also triggers a series of symptoms, which allows the organism to recognize what is happening and which act as a stimulant for preventative action (Sunisha Kulkarni, Drug Interaction; Ben D Snyder et al, 2012).

The overall effect of the addition of two drugs can be any of:

1. **Synergistic** (such a two drug combination leads to a larger effect than expected), or
2. **Additive** (the result expected when you add together the effect of each drug if taken independently) or,
3. **Antagonistic** (such a drug combination leads to a smaller effect than expected). Sometimes confusion may exist on whether drug effects are **either synergistic or additive, since the individual effects of each drug may vary from patient to patient.**

A synergistic interaction may be beneficial for patients, but on the other hand may also increase the risk of overdose or even adverse effects.

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Both synergy and antagonism can occur during different phases of the interaction between a drug, and an organism. For example, when synergy occurs at a cellular receptor level this is termed agonism, and the substances involved are termed **Agonists.** On the other hand, in the case of antagonism, the substances involved are known as **inverse agonists.** The different responses of a receptor to the action of a drug has resulted in a number of classifications, **such as "partial agonist", "competitive agonist" etc.** These concepts have fundamental applications in the pharmacodynamics of these interactions (Sunisha Kulkarni, Drug Interaction; Ben D Snyder et al, 2012).

MANAGING DRUG INTERACTION:

A. Avoid the combination by:

i. Endeavor to review the existing drug schedules, then

ii. Choose an alternative drug

B. Monitor the patient by checking the following:

i. Timing and introduction of interacting drug

ii. Patient characteristics

iii. Expected time course of interaction

iv. Concomitant illnesses

C. Adjust the doses of:

i. Either or both interacting drug

D. Maintain statuesque / Continue as before (Do nothing)

i. If the interaction is not that significant (Temi Abimbola, 2022).

PREVENTION OF DRUG INTERACTION (DI)

Ensure you take a full drug history including all the over-the-counter (OTC) and herbal products. Asses clinical risks of in the patient. It is worthy of note that critically ill patients who have multisystem disease with compromised pulmonary, cardiac, renal or hepatic function have an increased risk for drug interactions.

The following details are very necessary in prevention of drug interactions:

1. Confirm and document patient's drug / medication history
2. Minimize the number of drugs being taken (especially concurrent) by frequently reviewing the patient's drug list
3. Consider adverse drug interactions in the differential diagnosis whenever any change occurs in a patient's prescription course
4. Extra caution must be taken when prescribing medications with a low therapeutic index (theses are known to have a high risk for drug interactions e.g. Digoxin, a Cardiac Glycoside with a low therapeutic index).

Drugs with low “Therapeutic Index may include: Anticoagulants, Digoxin, Anti-arrhythmic agents, Lithium Carbonate, Theophylline, Oral Hypoglycemic agents, Anticonvulsants” (Temi Abimbola, 2022).

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Table 1. Drug classes and their examples with several narrow therapeutic index (object)

	DRUG CLASS	EXAMPLE
1.	**Antiarrhythmic class**	**Amiodarone**
2.	**Anticoagulant**	**Warfarin**
3.	**Antiepileptic's**	**Phenytoin**
4.	**Antineoplastic**	**Sunitinib**
5.	**Aminoglycoside antibiotics**	**Gentanicin**
6.	**Immunosuppressant's**	**Tacrolimus**

The therapeutic index is often easier to recognize than define, as the vulnerability of the patient as it affects the dose–response relationship. A clinical question that is very useful in identifying a narrow therapeutic index drug is: ***"Would doubling or halving the dose of this drug have a major effect on this patient"?*** (Ben D Snyder et al, 2012).

PREVENTING UNWANTED DRUG–DRUG INTERACTIONS CLINICALLY

Pharmacodynamic drug–drug interactions can be anticipated based on the knowledge of the clinical effects of the drugs involved. **"The better your pharmacological knowledge of the drugs involved, the easier is the prediction."** *Hence, the dictum is to Prescribe a few drugs that you know very well.*

Conversely, Pharmacokinetic drug–drug interactions are more difficult to anticipate since they are not predictable from the clinical effects of the drugs involved. Recognition of drugs that have a narrow therapeutic index (Table 1, above) and the major perpetrators of pharmacokinetic interactions will however, help in identifying most of these interactions. In this we make use of five 'rules' to manage potential drug–drug interactions clinically (Ben D Snyder et al, 2012):

1. Any interactions between existing drugs in a given patient have already occurred. Hence they are part of differential diagnosis.

2. Knowledge of the pharmacological effects of drugs and of patient physiology together allows recognition of potential pharmacodynamics of drug– drug interactions.

3. Drugs with a narrow therapeutic index are particularly susceptible to pharmacokinetic drug– drug interactions (see Table 1 above).

4. A small number of drugs are important 'perpetrators' of pharmacokinetic drug–drug interactions.

5. Starting or stopping a drug is a prescribing decision that may cause a drug interaction. Monitoring patients for drug toxicity or loss of efficacy is part of routine care. Checking for changes in symptoms, biomarkers of effect, or drug concentrations soon after prescription changes helps identify drug interactions early and can reduce harm (Ben D Snyder et al, 2012).

Table 2. Common Medication Interaction List

Medication and Herbal Interactions

Herb	Medication	Result
Aloe	Diuretics	Decreases potassium levels
Aloe	Steroids, hormones, laxatives	Decreases potassium levels

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Cayenne	Anticoagulants	Increases blood clotting time
Dong quai	Anticoagulants	Increases blood clotting time
Ephedra	High blood pressure	Increases blood pressure medications
Ephedra	Diabetic medications	Increases blood sugars
Garlic	Anticoagulants, aspirin	Increases blood clotting time
Garlic	Diabetic medications	Decreases blood sugars
Ginko biloba	Anticoagulants	Increases blood clotting time
Ginko biloba	Diuretics	Increase blood pressure
Ginseng	Digoxin (Lanoxin®)	Increase medication level
Ginseng	Anticoagulant	Increase blood clotting time
Ginseng	Estrogens	Increase medication level
Ginseng	High blood pressure medications	Increase blood pressure
Ginseng	Diabetic medications	Decreases blood sugar
Glucosamine	Diabetic medications	Alters blood sugar
Goldenseal	Sedatives	Increases sedative effect
Hawthorn	High blood pressure medications	Decreases blood pressure
Hawthorn	Digoxin (Lanoxin®)	Increases medication level
Kava-kava		Liver damage
Peppermint	Ulcer medications	Possible acid reflux
St. John's Wort	Steroids, antidepressant medications, theophylline, warfarin, cyclosporine, digoxin, invirase	Alters medication level
Valarian	Antidepressants, ethanol	Increases sedative effect.
Medication	**Medication**	**Result**
Antihistamine	Sedative medications	Increase sedative effect
Antacids	Antibiotics, digoxin, quinidine	Decreases medication effectiveness
Decongestants	High blood pressure medications	Increase blood pressure
Diphenhydramine	High blood pressure meds	Increase blood pressure
Ethanol	Sedative medications	Increase sedative effects
Warfarin	Aspirin, ibuprofen, naproxen	Increase blood clotting time
Viagra®	Nitroglycerin, isosorbide	Decrease blood pressure

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Medication –Food Interaction

Food	Medication	Result
Asparagus, spinach, broccoli	Anticoagulants	Decreases blood clotting time
Grapefruit	Statin medications	Interferes with medication levels

(Adopted from the: Minnesota Poison Control System. www.mnpoison.org).

CONCLUSION

To a major extent, **Positive drug interactions** can possibly be taken advantage of in Pharmacotherapy even as the Pathological significance of the **negative drug interactions** are usually of more interest clinically. The reason for the enhanced interest in the later is because they are often unexpected, and may even go undiagnosed. Studying the above conditions favoring the appearance of drug interactions can help in preventing them, or at least aid timely diagnosis of the same. The factors or conditions that predispose to the appearance of interactions may include: Poly pharmacy, Old age or much Younger ages, Genetic factors, Drug dependent factors like Narrow Therapeutic index, Steep Dose-response curve, Saturable hepatic metabolism, Renal diseases, Hepatic diseases and other major or serious diseases etcetera.

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